Abstracts

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AUTOTRANSPLANTATION FOLLOWING TOTAL PARATHYROIDECTOMY FOR RENAL OSTEODYSTROPHY. Donald A. Adams, Robert M. Gipstein, Morris T. Grabie, and Roscoe C. Webb*, Santa Monica, California

Severe renal osteodystrophy (RO) in chronic dialysis patients may require parathyroidectomy (PTX) when not controlled with 1,25-$(OH)_2$ Vit. D (D). RO symptoms may recur unless total PTX is done, but medical management is then more difficult. Autotransplantation (AT) of a piece of excised parathyroid tissue (PTT) into the forearm can make management less difficult and if hypertrophy occurs, allows easy access for excision. Advanced uncontrolled RO in 3 chronic dialysis patients was treated by total PTX and AT of ½ of a parathyroid gland, multisectioned and implanted subcutaneously into the forearm. These patients had received D and had calcium levels of 9.5-11.8 mg/dl and parathyroid hormone (PTH) levels of 1188-3900pg/ml (normal 10-80) pre-op. Post-op 1 patient had prolonged severe hypocalcemia, requiring large supplements of D and Ca, but after 12 mo began to show evidence of PTH production with only small doses of D and calcium needed. The 2nd patient 6 mo post-op had 130pg/ml PTH with normal serum Ca on minimal doses of D. The 3rd patient had post-op spontaneous rib fractures with PTH of 140pg/ml at 4 mo, 350pg/ml after 8 mo and because of increasing hyperparathyroidism, underwent resection of 3/4 of the forearm AT site which disclosed microscopically hyperplastic PTT. One mo later the PTH had decreased to 140pg/ml. These data indicate that AT of PTT for RO takes 4-12 mo to produce active PTH, that medical management may be simpler than after total PTX alone, and that the transplanted PTT may be easily removed if hyperparathyroidism recurs.

THE RENAL CONVERSION OF 25-HYDROXYVITAMIN D_3 TO 1,25-DIHYDROXYVITAMIN D_3 DECREASES WITH AGE IN THE RAT. H.J. Armbrecht, T.V. Zenser and B.B. Davis, VA Medical Center, St. Louis, MO. 63125.

The purpose of this study was to compare the capacity of the kidney to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, the physiologically active form of vitamin D, in young and adult rats. Young (1.5 months of age) and adult (12 months of age) rats were made vitamin D-deficient by feeding a low calcium, vitamin D-deficient diet for 6 weeks. The conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 was measured in the whole animal by administering a dose of tritiated 25-hydroxyvitamin D_3 and determining the appearance of tritiated metabolites in plasma and small intestine. In the adult rat, only 2.1±0.6% of the plasma radioactivity was in the form of 1,25-dihydroxyvitamin D_3 after 24 hours compared to 20.8± 3.0% in the young. The conversion of tritiated 25-hydroxyvitamin D_3 to its products was also measured directly in isolated slices of renal cortex. 1,25-Dihydroxyvitamin D_3 production by adult renal slices was found to be less than one-tenth that of slices from the young. Slices of renal medulla from the young rat produced only small amounts of 1,25-dihydroxyvitamin D_3 compared to slices of renal cortex. These results indicate that there is a marked decrease in the capacity of the vitamin D-deficient adult rat to convert 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3. These studies also demonstrate the usefulness of renal slices in measuring changes in the renal conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 in the mammal.

●THE EFFECTS OF ORAL PHOSPHATE SUPPLEMENTS (PRx) AFTER KIDNEY TRANPLANTATION (Tx). N.D. Adams, G.F. Carrera,* R.W. Gray,* W.F. Piering and J. Lemann, Jr. Depts. of Med., Radiol. and Biochem., Medical College of Wisconsin, Milwaukee, WI

Hypophosphatemia is common after Tx and has been attributed to residual hyperparathyroidism (HPT). PRx has been advocated to protect bone despite elevations of iPTH after acute PRx and the accepted role of P to produce secondary HPT. We studied 13 patients eating constant diets 9 to 78 months after Tx, either after 8 to 76 months ongoing PRx, 0.65 mmol/kg/day and then 2 months after stopping PRx (C; N=9) or during C and then after 2 to 3 months PRx (N=4). During C, U_PV averaged 28±5 SD and rose during PRx to 55±14 mmol/day;$p<0.001$. During C, C_{Cr}, fasting serum Ca, P and iPTH (COOH-antibody) averaged 66±19 ml/min/1.73 m^2, 2.71±0.22 mmol/L, 1.11±0.12 mmol/L and 51±36 µlEq/ml (normal 2 to 10) respectively and did not change during PRx. Integrated serum P throughout the day (6 measurements) rose from 1.06±0.13 (C) to 1.15±0.15 (PRx) mmol/L; $p<0.02$. Serum 1,25-$(OH)_2$-D fell from 116±51 (C) to 98±49 (PRx) pmol/L;$p<0.005$. Fasting TmP/GFR (Bijvoet nomogram) fell from 0.83±0.11 (C) to 0.70±0.14 (PRx) mmol/L;$p<0.001$ (normal=1.0 to 1.7). $U_{Ca}V$ fell from 4.3±3.1 (C) to 2.3±1.8 mmol/day;$p<0.01$. Neither E/F P nor TmP/GFR correlated to iPTH while serum Ca correlated positively ($r=0.64$). $U_{Ca}V$ directly correlated to serum 1,25-$(OH)_2$-D ($r=0.60$). Seven of the 13 had x-ray evidence of HPT bone disease that improved after Tx regardless of PRx. We conclude: 1)longterm PRx after Tx does not worsen HPT bone disease, 2) 2 to 3 months of PRx does not worsen HPT as judged by serum iPTH and 3) P homeostasis appears to be independent of iPTH and 1,25-$(OH)_2$-D.

●ROLE OF NICOTINE-ADENINE DINUCLEOTIDE (NAD) IN THE PHOSPHATURIC RESPONSE TO PARATHYROID HORMONE (PTH). Theresa J. Berndt*, Franklyn G. Knox and Thomas P. Dousa, Dept. of Physiol. & Biophysics, Mayo Clinic, Rochester, MN 55901 (intr. by J. A. Velosa)

Recent studies have suggested an important role for NAD in the intracellular control of proximal phosphate (Pi) reabsorption (Clin. Res. 28:452A, 1980.) The present studies were performed to evaluate the effect of nicotinamide (NiAm) treatment, shown to increase renal cortical NAD levels, on the phosphaturic response to PTH. Clearance studies were performed in TPTX rats stabilized on normal (NPD, 0.7%) or low (LPD, 0.07%) Pi diet injected with NiAm (i.p., 1g/kg) or vehicle 2 hours prior to anesthesia, and the response to PTH evaluated with subsequent determination of renal cortical $NAD^+/NADH$ levels.

		FE_p%†	$NAD^+/NADH$ ratio	
NP: (n=8)	Vehicle	4±1	2.4±0.2	(n=7)
	PTH	38±5§	3.5±0.4§	(n=8)
NP: (n=7)	NiAm	32±7	8.2±0.8	(n=7)
	PTH	76±6§	7.6±1.0	(n=7)
LP: (n=8)	Vehicle	0.10±.03	3.5±0.5	(n=8)
	PTH	0.14±.04	3.5±0.6	(n=5)
LP: (n=9)	NiAm	2±1	5.8±0.7§	(n=7)
	PTH	16±4§	8.3±0.7§	(n=8)

We conclude that NiAm 1) is a potent phosphaturic agent in rats fed NP diet, 2) enhances the phosphaturic effect of PTH, and 3) restores the phosphaturic response to PTH in rats fed LP diet, due to increased renal cortical NAD levels.

†FE_p = fractional excretion of phosphate

§$p<0.05$

EFFECT OF PHOSPHATE DEPLETION ON CELL MEMBRANE PHOSPHOLIPIDS AND GLUCOSE PATHWAY IN KIDNEY, LIVER AND SKELETAL MUSCLE. N. Brautbar, S. Moser,* P. Finander,* and S.G. Massry. Div. Neph., Dept. Med., USC Sch. Med., Los Angeles, CA.

Impaired resting membrane potential and cellular glucose uptake occur in phosphate depletion. To evaluate the possible mechanisms we examined the biochemical integrity of cell membrane and glucose pathways in cells of liver, kidney and skeletal muscle. Rats were raised on either normal (0.3%, NP) or low phosphorus diet (0.03%, LP) for 8 and 12 weeks. Acid extractable water soluble phospholipids were evaluated utilizing the Bessman Automatic Ashomatic phosphorus analyzer. A significant reduction in phospholipids occurred in only liver and kidney at 8 and 12 weeks from 19.2±0.9 to 16.7±0.6 and 15.9±1.3, and from 29.0±1.4 to 22.4±1.8 and 20.6±1.5 (SE) μmoles/gr protein ($p<0.01$), respectively. Glycogen content fell significantly in liver at 12 weeks of LP from 383±32 to 151±16 ($p<0.01$), and in muscle at 8 and 12 weeks from 59.8±11.6 to 35.6±3.0 and 35.0±2.1 μg/mg protein ($p<0.05$). Hexose-6-P concentration was significantly reduced in muscle at 8 and 12 weeks of LP from 3.9±0.4 to 2.1±0.2 and 2.4±0.2 μmoles/gr protein ($p<0.05$) but was not reduced in liver and kidney. Cellular Pi fell markedly in muscle and kidney at 8 weeks and in liver at 12 weeks. Thus, in LP there are: 1) impaired cellular glucose and glycogen metabolism resulting in reduced fuel for muscle contraction, and 2) impaired biochemical integrity of renal cell membrane. These derangements may provide at least partial insight into the mechanisms underlying skeletal myopathy and renal tubular transport defects seen in phosphate depletion.

EVIDENCE THAT GLUCOCORTICOID EXERTS A DIRECT INHIBITORY EFFECT ON RENAL PO_4 REABSORPTION. B. Eby*, J. Guntupalli*, and R. Lau (intr. by D. Lipschutz). Nephrology Division, University of Michigan, Ann Arbor, Michigan.

Considerable controversy exists in regard to the effects of glucocorticoid on renal PO_4 handling. To address this issue, the following clearance studies were performed during 10% volume expansion with saline. In intact rats, infusion of methylprednisolone (Medrol) at 2.5 mg/kg/h increased fractional excretion (FE) of PO_4 (14.1 to 19.6%) and decreased plasma PO_4 (7.8 to 6.6 mg%). In parathyroidectomized (PTX) rats, Medrol also increased FE_{PO_4} (8.04 to 15%) and decreased plasma PO_4 (14 to 11 mg%) without altering FE_{Na} (11.1 to 12.7%) while GFR tended to rise (2.0 to 2.3 ml/min). To evaluate the role of renal vasodilatation, clearance (C) of para-aminohippurate (PAH) was measured during four phases: baseline (B), infusion of Medrol (M_I), infusion of superimposed angiotensin II (M_I + AII) and after stopping AII but not Medrol (M_{II}). The results are: (* indicates $p<.05$ cf to baseline phase).

	B	M_I	M_{II} + AII	M_{II}
C_{PAH} (ml/min)	10.5	12.8*	10.9	12.4*
GFR (ml/min)	3.5	3.9*	3.7	4.3*
FE_{PO_4} (%)	3.0	9.4*	12.8*	12.2*

There was no change in plasma glucose during Medrol (112 vs 113 mg%) or in saline time control. Neither saline nor deoxycorticosterone acetate altered FE_{PO_4}. Conclusions: (1) Acute glucocorticoid infusion inhibits renal PO_4 reabsorption. (2) This seems to be a direct tubular effect since the phosphaturia is independent of PTH, plasma PO_4 or glucose and altered renal hemodynamics or Na excretion.

THE TURNOVER AND ACTION OF 1,25-DIHYDROXYVITAMIN D IN NORMAL MAN. J.W. Coburn, G.F. Bryce,* B.S. Levine, J.P. Mallon*, F.R. Singer*, & O.N. Miller* VA Wadsworth Med. Ctr., UCLA and USC Sch. Med. & Roche Research Ctr., Los Angeles, CA.

The pharmokinetics and actions of calcitriol (1,25) were studied in 14 volunteers given .25μg, .50μg, and 1.0μg, each with intervening 2 week control (C) periods. Serum (S)Ca, P, Mg, iPTH, and 1,25 were measured 12 hrs. after p.m. and 4 hrs after a.m. doses; urinary (U) Ca/creatinine (Cr), OHproline (HP)/Cr, P and Mg were measured during treatment and C periods. There were dose-related increments in UCa/Cr and SP; but SCa rose only after 1.0μg b.i.d.; UP, SMg, and UMg did not change.

DOSE	.25μg bid	.50μg bid	1.0μg bid
ΔUCa/Cr (mg/kg)	18±7*	+84±18**	113±21**
ΔUHP/Cr (μg/mg)	-3.4±1.2	-2.3±1.0*	-3.2±2.2
ΔSCa (mg/dl)	+0.06±10	+0.10±.08	+0.19±.08*
ΔSP (mg/dl)	+.21±.08*	+.25±.16	+.68± .14**
ΔSiPTH (μlEg/ml)	-1.1±.51*	-1.0±.49*	-.9±.14**
ΔS-1,25 (pg/ml)	+6±4	+13±2**	+16±3**

Δ = change in; Paired t: *$p<.05$, **$p<.01$

From baseline values of 39±4 pg/ml, S-1,25 rose by 13±3, 20±2 and 21±8 pg/ml 4 hrs after .25, .50 and 1.0μg, respectively; values after 12 hrs were increased only with .50 and 1.0μg (Table). After .50 and 1.0μg b.i.d., S-1,25 levels decayed to baseline with a $t_{½}$ of 3.5 hrs. Thus, the plasma turnover of 1,25 is short; it caused a dose-related rise in UCa but reduced SiPTH which probably accounts for the rise in SP and fall in UHP. The observed fall or lack of rise in UHP provides evidence that these doses of 1,25 do not augment bone resorption and UCa is due to higher Ca absorption.

MEASUREMENT OF SERUM IONIZED MAGNESIUM (Mg) IN ACUTE RESPIRATORY ALKALOSIS AND ACIDOSIS IN THE DOG. M.V. Feinroth,* M.Feinroth,* E.A. Friedman, and G.M. Berlyne. Downstate Medical Center, Brooklyn VA Medical Center, Brooklyn, NY.

Serum magnesium is found in three forms: protein bound, complexed, and ionized. We measured the changes in these fractions of magnesium in mongrel dogs in control conditions and after inducing acute respiratory alkalosis and acute respiratory acidosis. Each dog acted as its own control. Ionized magnesium was measured in ultrafiltrates of serum prepared under controlled pH conditions using a divalent cation electrode. The Wilcoxon test for paired data was used for statistical analysis.

(Mean ± SEM)	Acute Resp. Alkalosis (N=5)	Control (N=5)	Acute Resp. Acidosis (N=4)	Control (N=4)
Serum pH	7.69 ± .07	7.41±.02	7.16±.03	7.41±.02
Serum Ionized Mg (mmoles/L)	.37 ±.05	.26±.04 (2P = .06)	.22±.04	.37±.04
Serum Complexed Mg (mmoles/L)	.17 ±.05	.30±.03 (2P = .06)	.35±.06	.20±.05

Changes in whole blood pH are associated with changes in both serum ionized Mg and complexed Mg. The serum ionized Mg increased and the serum complexed Mg decreased in acute respiratory alkalosis. The reverse changes were seen in acute respiratory acidosis.

THE PRE-OPERATIVE ILIAC CREST BONE BIOPSY AS A PROGNOSTIC INDEX OF THE HYPOCALCEMIA INDUCED BY PARATHYROIDECTOMY. A.J.Felsenfeld*, J.M. Harrelson*, and R. A. Gutman, Depts. of Med. and Pathol., Duke Univ. and Univ. of Okla. Health Sci. Ctr. and VA Med. Ctrs. of Durham, N.C. and Okla. City, OK.

Nineteen maintenance dialysis patients underwent iliac crest bone biopsy (ICBB) prior to total parathyroidectomy (PTX) with forearm reimplantation of glandular tissue. Quantitative histomorphometric analysis revealed changes of renal osteodystrophy in all patients. Osteoclastic resorption occupied 9.5±5.1 (S.D.) percent of the trabecular surface (TS) - (normal<1%). The serum calcium concentration ($[Ca^{++}_S]$) fell post PTX and the maximum fall occurred within 7 days. The decrement of $[Ca^{++}_S]$ post PTX correlated with the severity of the pre-PTX bone resorption ($r=.77$, $p<.001$). The serum alkaline phosphatase rose in most patients post-PTX; the maximum level bore a significant positive correlation with the pre-PTX osteoblastic activity on ICBB ($r=.71$, $P<.001$). Moreover, the decrement of $[Ca^{++}_S]$ also correlated with pre-PTX osteoblastic activity ($r=.79$, $P<.001$) and with the change in alkaline phosphatase ($r=.59$, $p<.001$).

These data suggest that the patients with the greatest degree of osteoclastic bone resorption have the sharpest fall in $[Ca^{++}_S]$ and the greatest rise of alkaline phosphatase after PTX. Although the mechanism for the relationship is not clear, we suggest the removal of the source of parathyroid hormone leads to uncoupling of bone resorption and formation. Bone formation appears to continue as demonstrated by the rise in alkaline phosphatase.

THE ABSENCE OF A ROLE FOR PARATHYROID HORMONE (PTH) IN BUFFERING CHRONIC ACID LOADS. D.S. Fraley and S. Adler. Montefiore Hospital, Univ. of Pittsburgh, School of Medicine, Pittsburgh, PA.

We previously demonstrated that thyroparathyroidectomized (TPTX) nephrectomized rats did not buffer a portion of acutely administered acid. To determine whether PTH altered tissue buffering and urinary acid excretion in rats with normal renal function given acid chronically, 13 normal (N) and 11 PTX (P) rats were initially tube fed dextrose for one day. Blood pH was 7.41 ± .02 and 7.42±.02 (S.E.M.) in N and P rats respectively ($p > 0.5$) but blood bicarbonate ($HCO_3)_B$ was lower in P; 20.5±.09 vs. 22.9 ± .06 ($p < .025$). Blood calcium in N was 9.1 ± 0.2 and 5.1 ± 0.1 in P ($p < .001$). Baseline 24 hour urinary net acid excretion (NAE) was determined and then rats were tube fed 6,000 µmoles of NH_4Cl daily for three days. The results are shown in the table with Δ indicating total changes from baseline for the three days of acid loading.

	Δ $(HCO_3)_B$ mEq/l	Baseline NAE ---------µmoles----	Δ NAE	% acid load excreted
N	-2.6	1524±268	9402±1143	52.2±6.4
P	-2.3	1248±159	10,496±644	57.9±3.6
p	> 0.4	> 0.2	> 0.4	> 0.4

Calculated tissue buffering of 47.4% in N and 41.7% in P were not significantly different ($p > 0.3$). Thus, when renal function is normal a large portion of chronic acid loads are buffered intracellularly. In contrast to results in nephrectomized rats absence of PTH does not affect this tissue buffering. Moreover, urinary acid excretion is not significantly altered by PTH deficiency.

● $24,25(OH)_2D_3$ ENHANCES BONE FORMATION IN UREMIA IN THE ABSENCE OF AN EFFECT ON PTH SECRETION. D. Finco, K. Olgaard, M. Rothstein*, J. Schwartz*, A. Korkor*, S. Teitelbaum*, S. Klahr, and E. Slatopolsky. Washington University School of Medicine, St. Louis, Missouri.

The effects of $24,25(OH)_2D_3$ on parathyroid gland function and bone remain controversial. These effects were studied in vitro using normal bovine dispersed parathyroid cells, and in vivo in uremic dogs with secondary hyperparathyroidism. The secretion of PTH by the parathyroid cells responded appropriately to low (0.5 mM), normal (1.2 mM), and high (3.0 mM) Ca^{++} concentration in the medium. However, addition of 100 to 1000 nM $24,25(OH)_2D_3$, for as long as 300 minutes, had no effect on PTH release or cAMP production from these cells. In the in vivo studies, 5 chronically uremic dogs received 2.5 µg of $24,25(OH)_2D_3$ per day orally for 6 months, while 6 uremic dogs served as controls (C). Bone biopsies were obtained after 6 months in both groups. The two groups had similar values for creatinine clearances, intestinal calcium absorption and levels of plasma total calcium, ionized calcium, and phosphorus. After 6 months of treatment the iPTH levels were 252 ± 74 µlEq/ml in C and 331 ± 83 µlEq/ml in the treated group (normal range 10-60). However, as compared to the untreated uremic dogs, the treated animals had an increase of approximately 50% in bone forming surfaces ($p<.01$), while the number of osteoclasts were normal. In conclusion, $24,25(OH)_2D_3$ had no influence on the secretion of PTH in vitro or in vivo. However, $24,25-(OH)_2D_3$ had a marked effect on uremic bone histology with an increase in bone forming surfaces.

● PREVENTION OF PHOSPHATE INDUCED NEPHROCALCINOSIS IN EXPERIMENTAL RENAL INSUFFICIENCY BY PHOSPHOCITRATE. Luis Gimenez,* William Tew,* Judith Hermann,* and W. Gordon Walker. The Johns Hopkins Hospital, Baltimore, Maryland.

High phosphate diet deposits calcium phosphate in kidneys of partially nephrectomized rats produced progressive loss of renal function; conversely reduced phosphate intake prevents progression of renal damage. Such phosphate reduction may well prevent progressive destruction in humans with damaged or diseased kidneys. This adverse effect of calcification could possibly be prevented by phosphocitrate, a compound we recently synthesized and demonstrated to be a strong inhibitor of calcium phosphate crystallization (Tew, et al, Biochem. 19:1983-1988, 1980). Its utility in renal failure was evaluated in rats subjected to removal of 1 and 2/3 kidneys and fed 7+ mmol PO4/day for 44 days with the following results:

RENAL CA++ mmol/100 gm KIDNEY (mean±SEM)

	CORTEX	MEDULLA
Control	.37±.07	.57±.11
↑PO4	7.80±2.3	9.90±4.5
↑PO4+pCit	1.26±.68	1.54±.53

Renal tissue from phosphocitrate treated animals had significantly less calcium than animals receiving ↑PO4 alone when tested both by non-parametric methods and by Student's t ($p<.01$ and $<.025$ respectively). Further study is warranted to evaluate the potentially useful therapeutic role for phosphocitrate suggested by these data in preventing the progressive renal damage associated with increased phosphate intake and hyperphosphatemia.

HYPERCALCEMIA INDUCED BY CHRONIC HYPERPARATHYROIDISM OR BY 1,25 DIHYDROXYCHOLECALCIFEROL (1,25 D) RESULTS IN METABOLIC ALKALOSIS. A. Greenberg,* P.D. Mitnick, T. Coffman,* C.J. Wolf, and S. Goldfarb. Renal Electrolyte Section, Dept. of Medicine, Univ. of Pa., Philadelphia, Pa.

To investigate the effect of PTH and calcium on renal acid handling, we studied two models of hypercalcemia in the rat. Inbred rats made hyperparathyroid (HPTH) by autologous transplantation of 24 parathyroid glands developed hypercalcemia (plasma calcium (P_{Ca}) 5.48±0.03 vs. 4.96±0.06 mEq/L, $p<0.001$) and metabolic alkalosis (plasma total CO_2 (TCO_2) 25.44±0.47 vs. 23.84±0.57 mEq/L, $p<0.05$; plasma pH 7.44±0.01 vs. 7.39±0.02, $p<0.05$, day 7) as compared to pair fed controls (C). Total acid excretion (TAE) was greater in HPTH rats (574.3±71.8 vs. 280.8±31.9 µEq/24°, $p<0.001$) as was titratable acid. Ammonium excretion was similar but urine pH and bicarbonate were significantly lower in HPTH than in C rats. In the second model, rats were treated with daily i.p. injection of 40 ng 1,25 D (Vit D rats) and compared to pair fed sham injected controls (NoD). Vit D rats developed hypercalcemia (P_{Ca} 6.66±0.11 vs. 5.62±0.01 mEq/L, $p<0.001$) and metabolic alkalosis (TCO_2 28.88±0.44 vs. 25.91±0.36 mEq/L, $p<0.001$, day 10). TAE was greater in the Vit D rats (1447.5±86.7 vs. 330.1±42.6 µEq/24°, $p<0.001$) as was titratable acid. Ammonium excretion was similar in Vit D and NoD rats but urine pH and bicarbonate were significantly lower in Vit D rats. Thus chronic hypercalcemia produced by parathyroid transplantation or by 1,25 D administration resulted in metabolic alkalosis with augmented renal acid excretion. This suggests a specific effect of calcium on renal acid handling.

KIDNEY TRANSPLANT RECIPIENTS: HYPOPHOSPHATEMIA AND BONE DISEASE. J.M. Harrelson*, A.J. Felsenfeld*, F. Llach, and R.A. Gutman. Depts. of Med. and Pathol., Univ. of Okla. Health Sci. Ctr. and Duke Univ., and VA Med. Ctrs. of Okla. City, Okla. and Durham, N.C.

Hypophosphatemia occurred in 43 of 88 kidney transplant recipients. To study the mechanisms of hypophosphatemia and its effects on bone, 6 hypophosphatemic patients were evaluated. They received their transplanted kidneys 3 to 14 years previously and the creatinine clearances ranged from 53 to 81 cc/min; doses of prednisone were < 17.5 mg qd. Significant mean (± SD) serum values were: phosphorus 1.8 mg/dl ± .2; calcium 9.6 mg/dl ± .3 and alkaline phosphatase 82 IU ± 29. The mean 24 hour urinary calcium was 103 mg ± 51 and the $TmPO_4/GFR$ 1.8 ± 0.4 mg/dl (normal 2.5-4.2). The C-terminal parathyroid hormone (PTH) was 0.106 ± .07 ng/ml (normal < 0.1). Bone histomorphometric findings were:

	Patients	Normals
Osteoid surface (% total)	25 ± 11	9.3 - 25.5
Osteoid area (mm^2)	0.6 ± 0.2	0.1 - 1.0
Bone area (mm^2)	20 ± 3	17 - 31
Osteoclasts/mm^2	0.08 ± 0.1	0 - 0.1
Active resorption surface (% total)	0.3 ± 0.5	0 - 0.3
Mineralization	> 70%	> 70%

Our data suggest that hypophosphatemia in kidney transplant recipients: 1) is a frequent and persistent finding; 2) may be secondary to a non-PTH mediated renal phosphate leak; and 3) appears to produce only minimal changes in bone histomorphometrics and does not impair bone mineralization.

ON THE PHOSPHATURIA PRODUCED BY NH_4Cl ADMINISTRATION: INTERACTION WITH PTH AND DIET PO_4: EVIDENCE FOR THE ROLE OF ACIDEMIA. J. Guntupalli*, B. Eby*, and K. Lau (intr. by R. Swartz). Nephr. Division, University of Michigan, Ann Arbor, Mich.

The effects of metabolic acidosis on renal PO_4 handling are controversial. To test the hypothesis that NH_4Cl per se alters PO_4 excretion and to define the mechanism(s), clearance experiments were performed in volume-expanded rats. (1) In intact and PTXed rats, NH_4Cl (3.7 mM/kg/h) increased PO_4 clearance (C) (276 to 390 and 156 to 295 µl/min respectively) and fractional excretion (FE) of PO_4 (8.8 to 13.9% and 5.5 to 12.3% respectively). Both plasma PO_4 (10.6 to 9.6 mg%) and GFR (2.8 to 2.5 ml/min) fell. (2) Saline loading that doubled the FE_{Na} produced in NH_4Cl treated rats failed to alter PO_4 excretion. (3) Both lactic acid and HCl similarly increased C_{PO_4} and FE_{PO_4}. (4) Infusion of neutral agents (NH_4HCO_3 and glutamine) elicited no changes in plasma pH or PO_4 excretion. (5) At the peak effect of NH_4Cl, neutralization of the acidemia by $NaHCO_3$ reduced FE_{PO_4} (17.8 to 7.1%) to control. ΔFE_{PO_4} was inversely related to plasma pH. (6) PTH (3.3 units/kg/h), superimposed on maximal effective dose of NH_4Cl (5.7 mM/kg/h), further increased FE_{PO_4} (24.3 to 46.9%). (7) In PO_4 deprived rats, the effects of NH_4Cl were not blunted. (ΔFE_{PO_4} = 23 vs 21% in PO_4 repletion) and synergism with PTH was again evident (FE_{PO_4} from 19.3 to 32.4%). Conclusions: (1) These findings provide the first direct demonstration that NH_4Cl enhances PO_4 excretion independent of PTH, the NH_4 ion, increased NH_3 or Na excretion, plasma and diet PO_4. (2) Our data indicate that acidemia per se mediates the phosphaturia and by a mechanism fairly distinct from that of PTH.

FURTHER STUDIES WITH CIMETIDINE (C) IN UREMIC DOGS A.I. Jacob, P.W. Lambert*, J.M. Canterbury*, G. Gavellas* and J.J. Bourgoignie. (intr. by E. Perez Stable). Univ. of Miami School of Medicine, Miami, Florida.

We have previously reported that C reduces circulating iPTH in hemodialysis patients and in chronically uremic dogs. In five uremic dogs iPTH decreased from 536±70 to 157±32 µlEq/ml ($p<.01$) after twenty weeks of C treatment. Calcium balance was -369±119 mg/72 hrs before therapy and became +1141±409 mg/72 hrs ($p<.05$) after C. Concomitantly, serum phosphorus decreased from 5.7±.9 mg/dl to 3.4±.2 mg/dl ($p<.05$) but creatinine clearance, serum ionized calcium and phosphorus balance were unchanged. To determine if the decrease in iPTH was secondary to decreased glandular secretion or accelerated peripheral metabolism, pooled serum samples obtained before and after C were chromatographed on Bio-Gel P10 and the eluates assayed for immunoreactivity. C therapy decreased immunoreactivity of intact PTH and of lower MW PTH fragments. This indicates inhibition of glandular secretion. To determine the source of the changes in Ca balance we assayed vitamin D metabolites before and after C. Serum $1,25(OH)_2D$ increased in all dogs from 33.4±4.3 pg/ml to 51.8±2.4 pg/ml ($p<.01$) and $24,25(OH)_2D$ decreased from 2.4±.3 ng/ml to 1.9±.2 ng/ml ($p<.05$).

The effects of C in uremic dogs may be viewed as follows. C directly decreases PTH secretion. As a result, less phosphorus is lost from bone, and serum phosphorus concentration decreases. Because serum phosphorus is a modulator of renal 1α-hydroxylase activity, $1,25(OH)_2D$ levels subsequently increase, a positive calcium balance ensues and eucalcemia is maintained.

TOLUENE-INDUCED CALCIURIA AND MAGNESURIA IN RATS. W.D. Kaehny, R. Marzec-Calvert*. VA Medical Center, U. of Colorado Health Sciences Center, Denver, CO.

We exposed rats to toluene vapor during 7 days to determine the effect on renal function of this commonly abused inhalant. 11 rats were studied in metabolic cages after 4 hours of exposure to toluene in a chamber daily. All rats were pair-fed with normal controls who were handled similarly but with no toluene exposure. 6 rats were allowed water ad lib, 5 were pair-watered. Measured chemical variales did not differ between the groups, thus they are considered together. Final plasma values were:

	creat	pH	K	Na	Cl	Ca	Mg	P
CONT	0.4	7.39	4.5	139	113	9.8	1.7	7.5
EXP	0.5	7.37	4.0	142	112	9.9	1.7	8.2

None of these means differ between groups. Mean urinary excretions are given in µg (creatinine, Ca, Mg, P) or µeq/24h (Na, K, Cl):

	creat	K	Na	Cl	Ca	Mg	P
CONT	8038	2611	1035	1589	449	2904	18978
EXP	8223	2064[a]	733[a]	1525	1721[a]	5594[a]	21618

([a]=different from control, P<0.001 in each case.) Experimental rats had greater weight loss than control rats despite successful pair-feeding: 76± 19 vs 34±21 g (P<0.001). Diarrhea was not observed, however feces were not analyzed for weight or chemical composition. Thus Ca and Mg excretions were increased markedly while Na and K excretions were decreased. Filtered loads of Ca and Mg did not appear increased although daily estimates were not made. In conclusion, toluene inhalation affects Ca and Mg metabolism in a major way by undefined mechanisms which may iclude increased gut absorption, increased bone release or decreased renal reabsorption. The effect may be direct (membrane effect) or indirect (via chemical mediators).

●TUBULAR MECHANISMS FOR THE PHOSPHATURIC EFFECTS OF NH_4Cl ADMINISTRATION. K. Lau and B. Eby*. Nephr. Div., Dept. of Med., Univ. of Mich., Ann Arbor, MI.

Previous studies from this laboratory indicate that NH_4Cl infusion increases PO_4 excretion independent of plasma PO_4, parathyroid hormone (PTH) and the status of PO_4 balance. To define the tubular mechanism, clearance and micropuncture studies were performed on 4 groups of rats representing 2 relatively antiphosphaturic models (acute PTX and PO_4 deprivation). Group 1: Rats fed 0.6% PO_4 diet, acutely PTXed and undergoing 10% volume expansion with 150 mM/L NaCl. Group 2: Same as 1, but expanded with NaCl (93 mM/L) + NH_4Cl (57 mM/L). Groups 3 and 4: Rats chronically PTXed, fed PO_4 deficient diet (≤.03%) for 60 hrs before studies. Group 3 was treated as in Group 1 and Group 4 as in Group 2. Mean values for plasma (P) PO_4, tubular fluid (TF), inulin (In), and fractional delivery (FD) to late proximal (LP), early (E) and late (L) distal (D) tubules are as follow: *, p<0.05 and ‡, p<0.005 cf to preceding group.

	GFR (ml/min)	P_{PO_4} (mg%)	LP $\frac{TF}{P}_{In}$	FD_{PO_4} (%) LP	ED	LD	Urine
I	2.7	7.5	1.9	18	10	0.4	0.5
II	2.8	10	1.8	36*	21‡	14‡	13‡
III	2.7	8.6	2.0	35	16	8.3	0.8
IV	1.9	8.9	1.9	47‡	32‡	25‡	18‡

Conclusions: (1) In two relatively antiphosphaturic models, NH_4Cl inhibits PO_4 transport in the proximal convoluted tubule independent of fluid reabsorption. (2) This effect is sustained in subsequent nephron segments to produce a phosphaturia. (3) These tubular effects are independent of PTH, plasma and dietary PO_4.

●NICOTINAMIDE-ADENINE DINUCLEOTIDE (NAD) AS A CELLULAR REGULATOR OF RENAL PHOSPHATE (Pi) TRANSPORT. S.A. Kempson, S.-Y.L. Ou,* and T.P. Dousa. Mayo Clinic and Foundation, Rochester, MN.

NAD specifically inhibits Pi uptake by renal brush border membrane (BBM) vesicles in vitro (Clin. Res. 28:452A, 1980). Further, we observed that [^{3}H]-NAD binds in time-dependent way on BBM, either in the presence or absence of Na^+. Next we studied effects of in vivo increases of NAD in renal cortex (RC), elicited by i.p. injection of nicotinamide (NiA), upon BBM uptake of Pi and urinary Pi excretion ($U_{Pi}V$). Injection of 1 g/kg of NiA to thyroparathyroidectomized rats, stabilized on low Pi diet, resulted in increase of NAD^+ level (Δ+290%; P<0.001) a lesser increase in NADH, (Δ+45%; P<0.005) and in increase of NAD^+/NADH ratio (Δ+163%) in RC; tissue levels of ATP or cAMP did not change. Na^+-dependent ^{32}Pi uptake by BBM from the NiA-treated rats was decreased (Δ-39%; P<0.001) but uptake of [^{3}H]-D-glucose and uptake of $^{22}Na^+$ were unchanged. NiA injection elicited striking (20 x) increase in $U_{Pi}V$, but no increases in excretion of Na^+, K^+, Ca^{2+} and creatinine. NiA effects were dose-dependent (0.25-1.0 g/kg). Rate of BBM uptake of Pi (but not D-glucose) was inversely proportional to NAD^+ content (r=-0.77; P<0.001) and to the NAD^+/NADH ratio (r=-0.72; P<0.001) in RC. $U_{Pi}V$ was positively correlated with NAD^+ (r=+0.88; P<0.001) and inversely correlated with BBM uptake of Pi (r=-0.67; P<0.01). Results show that changes in endogenous RC tissue NAD are associated with decrease in BBM uptake of Pi and increase in $U_{Pi}V$. These observations support our hypothesis that NAD^+ in proximal tubular cells modulates Pi uptake across luminal BBM and consequently proximal tubular Pi reabsorption.

THE EFFECT OF 1,25-DIHYDROXYVITAMIN D_3 AND GLUCOCORTICOIDS ON TRANSEPITHELIAL CALCIUM AND PHOSPHATE TRANSPORT. D.B.N. Lee, V. Silis,* B.S. Levine, F.A. Eshaghpour* & J.W. Coburn. VA Wadsworth Med Ctr & UCLA Sch Med, Los Angeles, CA.

The effect of glucocorticoids (G) on transepithelial Ca and P transport has not been rigorously analyzed. We report the effect of pharmacologic doses of 1,25-dihydroxyvitamin D_3 (1,25D, 270ng/ day) or G (Decadron®, 1.2mg/day), given for 4 days, on Ca and P transport in descending colon of 250g rats. Controls received appropriate vehicle. Ca and P fluxes were measured with a modified Ussing technique with ^{45}Ca and ^{32}P and Krebs-Ringer-HCO_3 buffer containing glucose. Both 1,25D and G increased Ca absorption by stimulating absorptive flux (Jms) from 31±2 to 49±2 and from 22±2 to 40±3 nmoles/cm^2/hr, respectively (p<.01); secretory flux (Jsm) was unaffected. 1,25D had no effect on P transport, but G augmented net P secretion by stimulating Jsm. G increased the transepithelial short-circuit current (SCC) from 30±5 to 111±13 µA/cm^2 (p< 0.01), reflecting stimulation of Na transport; 1,25D had no effect. Increased Ca absorption was not correlated with the increase in SCC; thus G mimics 1,25D in stimulating active Ca absorption via a process not directly related to stimulated Na transport. The observations suggest that either a single Ca transport process may respond to both 1,25D and G, or each hormone may stimulate separate Ca transport processes. The physiological role of P secretion by the colon requires further studies.

MECHANISM OF HYPOPHOSPHATEMIA (SP↓) DURING ACUTE HYPERVENTILATION (AH). H. Leibovici, N. Brautbar, P. Finander,* and S.G. Massry. Div. Neph., Dept. Med., USC Sch. Med., Los Angeles, CA.

SP↓ occurs during AH. It was suggested that SP↓ is due to shifts of phosphorus from blood to cells secondary to increased glycolysis. Changes in serum phosphorus, muscle inorganic phosphorus (Pi) and phosphorylated intermediates were examined in 3 groups of dogs during 1) AH, 2) AH + IV glucose, 3) IV glucose only. Blood samples and muscle biopsies were taken at 0,1,2 and 3 h. SP↓ did not occur during AH or IV glucose but developed during AH + IV glucose; during the latter, serum phosphorus fell from 4.3±0.2 to 2.3±0.1 (SE) mg/dl at 3 h ($p<0.01$). Muscle Pi did not increase with IV glucose but rose with AH from 20.7±0.73 to 44.7±2.5 and with AH + IV glucose to 54.3±6.8 µmoles/g protein ($p<0.01$). Muscle hexose-6-phosphate did not increase with IV glucose but rose with AH from 6.2±0.8 to 10.8±1.8 and with AH + IV glucose to 12.8±2.0 µmoles/g protein ($p<0.01$). Lactate production increased markedly with AH from 0.43±0.03 to 1.05±0.15 and with AH + IV glucose to 1.72±0.28±SE mEq/l ($p<0.05$). The changes in serum phosphorus correlated with the changes in muscle hexose-6-phosphate and serum lactate. These data suggest: 1) AH causes a rise in serum lactate and increases both muscle glycolysis and Pi content; these changes are greater with AH + IV glucose, 2) SP↓ occurs only during AH + IV glucose. The results demonstrate that SP↓ of AH is due to shifts of phosphorus into cells secondary to increased muscle glycolysis. For SP↓ to develop during AH, elevated blood glucose levels must be present.

● EARLY RENAL BRUSH BORDER ADAPTATION TO DIETARY PHOSPHORUS RESTRICTION. B.S. Levine, A. Hodsman*, K. Ho,* H.F. Shaw,* B. Hirayama,* I. Kippin,* D.B.N. Lee, and J.W. Coburn. Depts. Med. & Physiol., VA Wadsworth Med. Ctr., Cedars-Sinai Med. Ctr. & UCLA Sch. Med., Los Angeles, CA.

Increased renal alkaline phosphatase (ALK-p'tase) is thought to play an important role in the renal adaptation to a low phosphate (P) diet. The present study evaluated P uptake by brush border membrane (BBM) vesicles and ALK-p'tase activities in BBM fractions from kidneys of rats fed a normal (0.6%) or low (0.03%) P diet for only 16-24 hrs. Serum P was 9.7±0.1 and 5.9±0.6 mg/dl after this period on normal or low P diet, respectively. Over the 24 hours, urinary P/creatinine was 7.4±0.8 with a normal P diet and 1.0±0.2 with the low P diet ($p<.01$). After 2 min of incubation, the ^{32}P uptake by BBM from rats ingesting a normal or low P diet was 1531±98 and 2112±183 pmol/mg protein, respectively ($p<.025$); peak glucose uptake was 226±17 and 209±42 pmol/mg protein, respectively. In kinetic studies, Km values were similar in the two dietary groups, but V max increased with the low P diet. ALK-p'tase BBM activities were not different, 865±62 and 831±51 nmol/min/mg protein, with the respective diets. In contrast, ALK p'tase activity increased 43% after 14 days of P-depletion. Thus, the renal conservation of P and adaptation to P-depletion appears within 16 hours of dietary P-restriction. The early reduction in urinary P in response to P-deprivation may not be due solely to reduced filtered P but involves changes in tubular BBM and occurs before ALK-p'tase activity increases. Increments in BBM ALK-p'tase are not required for the renal conservation of P.

● THE EFFECTS OF CHRONIC ORAL 1,25-$(OH)_2$-VITAMIN D_3 AMINISTRATION IN HEALTHY ADULTS. J. Lemann, Jr., N.D. Adams and R.W. Gray.* Depts. of Med. and Biochem., Medical College of Wisconsin, Milwaukee, WI.

We studied 6 healthy men eating constant diets providing 19.3±0.3 SD (NC) and 4.2±0.4 (LC) mmol Ca /day during control and during an 8 day period beginning 4 days after subject pairs were begun on 0.25, 0.5 or 0.75µg oral calcitriol at 0600, 1200, 1800 and 2400 hours. Blood was drawn at 0600, 1000, 1600, 2000 and 0600 after 3 days on each diet. Control serum 1,25-$(OH)_2$-D levels averaged 89±19 (NC) and 111±22 pmol/L (LC); $p<0.05$. Stable serum 1,25-D levels were achieved during calcitriol in proportion to log dose: 0.25µg:121, 0.5µg:186 and 0.75µg: 206 pmol/L. Integrated serum Ca rose from a control of 2.42±0.08 mmol/L in proportion to serum 1,25-$(OH)_2$-D ($r=0.77$) but did not exceed 2.60 mmol/L. iPTH fell as serum Ca rose ($r=-0.77$). Fasting serum Ca did not change. $U_{Ca}V$ rose in direct proportion to serum 1,25-$(OH)_2$-D on both LC (slope 0.043 mmol/day per pmol/L; $r=0.83$) and NC (slope 0.081 mmol/day per pmol/L; $r=0.94$) reaching a peak of 15.8 mmol/day at the highest calcitriol doses on NC. During calcitriol on LC, $U_{Ca}V$ averaged 7.3±2.7 mmol /day or 178±52% of diet Ca. Fasting U_{Ca}/creatinine also depended on serum 1,25-$(OH)_2$-D ($r=0.67$) and when 1,25-$(OH)_2$-D exceeded 140 pmol/L (normal mean + 2SD) averaged 0.39±0.06 mmol/mmol, above the normal mean + 2SD of 0.34 mmol/mmol; $p<0.05$. Neither serum creatinine or P, urine P, Mg, oxalate or fasting TmP/GFR changed during calcitriol while serum Mg fell by -0.05±0.01 mmol/L; $p<0.01$ on both diets. We conclude that when serum 1,25-$(OH)_2$-D levels are high, increased $U_{Ca}V$ on NC reflects enhanced intestinal Ca absorption but increased $U_{Ca}V$ on LC reflects enhanced bone resorption.

RENAL EXCRETION OF DICHLOROMETHYLENE DIPHOSPHONATE (Cl_2MDP). A. Licht and R.A. D'Amato*. Nephrology Division, UCLA School of Medicine, Los Angeles, CA. and Procter and Gamble Co., Cincinnati, Ohio.

Of the three diphosphonates in clinical use, Cl_2MDP presently appears to have the widest therapeutic applications. This compound is not metabolized and about half is taken up by the skeleton; the rest is excreted unchanged in the urine. Since existing data suggests that diphosphonates including Cl_2MDP are actively secreted by the kidney, the present studies were designed to define further the mechanism of renal excretion of Cl_2MDP as well as its influence on calcium, phosphate and magnesium excretion. Clearance experiments were performed before and during IV infusion of 5, 100 and 500 µmol/kg/hr of Cl_2MDP in unanesthetized rats. At all 3 levels, GFR and urinary volume remained constant. The ultrafilterable fraction of Cl_2MDP was 94±3% and the fractional excretion (FE) of Cl_2MDP has been found to be lower than unity.

Cl_2MDP µmol/kg/hr	GFR ml/min C	E	FE_{Cl_2MDP}%
5	2.02	2.04	80.2
100	2.04	2.07	92.6
500	1.88	1.88	90.4

C=Control; E=Experimental Values.

The lower doses of Cl_2MDP (5, 100) induced no significant changes in urinary excretion of phosphate, calcium or magnesium. However the highest dose caused a significant increment in the excretion of calcium and magnesium. Thus in these experiments we demonstrated reabsorption of Cl_2MDP which appears to be active and saturable, but no evidence of net secretion was observed.

● RHABDOMYOLYSIS INDUCED ACUTE RENAL FAILURE (ARF): INTERACTIONS OF CALCIUM (Ca), PARATHYROID HORMONE (PTH), 25 HYDROXYCHOLECALCIFEROL ($25D_3$) AND 1,25 DIHYDROXYCHOLECALCIFEROL ($1,25D_3$). Francisco Llach, Arnold J. Felsenfeld,* and M.R. Haussler.* Department of Medicine, Univ. of Okla. Health Sci. Ctr and VA Med. Ctr., Okla. City, OK. and Dept of Biochem., Univ. of Ariz., Tucson, AZ.

Abnormalities in Ca metabolism are frequent in rhabdomyolysis induced ARF. Six patients developed ARF secondary to rhabdomyolysis. Initial mean serum (S) creatinine was 17±3 mg/dl, uric acid 18± 3 mg/dl and CPK was > 12,000 in all 6 patients. Mean biochemical S findings (±SD) in the oliguric (I), early polyuric (II) and late polyuric phase (III) are shown in the following table:

	Sca mg/dl	Sp mg/dl	C-PTH ng/ml	$25D_3$ ng/ml	$1,25D_3$ pg/ml
I.	5.9±.9	19±1	1.2±.2	17±5	18±5
II.	10.9±1	6±.8	1.7±.3	22±11	65±6
III.	10.1±.4	3.9±.5	0.6±.1	32±15	50±8

The following are normal values: $25D_3$ (15-80 ng/ml), $1,25D_3$(20-50 pg/ml) and C-terminal PTH (<0.4 ng/ml).

In summary: In rhabdomyolysis induced ARF: 1) the initial hypocalcemia is associated with low 1, $25D_3$ and high PTH levels; 2) in the early polyuric phase the hypercalcemia was accompanied by increases in $1,25D_3$ and PTH levels and; 3) in the late polyuric phase Sca and $1,25D_3$ levels returned to normal.

Conclusions: a) The hypocalcemia of the oliguric phase may be secondary to decreased synthesis of $1,25D_3$ by the injured kidney; b) the hypercalcemia of the polyuric phase may be in part due to an increased synthesis of $1,25D_3$ resulting from the high PTH levels and recovery of renal function.

● ENHANCEMENT OF OSTEOCLAST-PRECURSOR-MEDIATED BONE RESORPTION IN VITRO BY GLUCOCORTICOIDS. J.D. Malone, A.J.Kahn*, S.L. Teitelbaum, Washington University Medical Center, St. Louis, Missouri.

Glucocorticoid-induced osteopenia is potentially among the most severe complications following renal transplantation. However, because cell cultures of osteoclasts are not available for analysis, it has not been possible to establish whether this osteopenia is the consequence of 2° hyperparathyroidism or is due to the direct action of glucocorticoids on bone resorption. We have recently shown that human monocytes and rodent peritoneal macrophages resorb bone in an osteoclast-like manner by a process which is sensitive to $1,25(OH)_2D_3$, 25 OHD_3 and calcitonin. Using pure (99%) populations of these surrogate osteoclasts, we have addressed the issue of whether glucocorticoids directly enhance bone resorption. Elicited rat macrophages, in vitro, mobilize a net 10-20% ^{45}Ca from isotopically-labeled bone within 4 days of culture. The addition of cortisol in concentrations as low as 10^{-8}M significantly (P<.001) increases isotope mobilization with optimum enhancement occurring at 10^{-6}M. Cortisol stimulation of macrophage-mediated bone resorption is associated with elevated protein and RNA synthesis as evidenced by a significant (P<.001) elevation in both ^3H-leucine and ^3H-uridine incorporation into treated cells. This association is also underscored by the observation that increased protein and RNA synthesis, and enhanced mineral mobilization are inducible phenomenon; i.e., phenomena that can be observed 48-72 hours after cells are pre-treated with cortisol for 4 hours. We conclude, therefore, that glucocorticoids directly stimulate both the metabolism and matrix-degrading activity of bone resorbing cells.

EXPERIMENTAL PRODUCTION OF CALCIUM OXALATE (CaOx) AND CALCIUM PHOSPHATE (CaP) CRYSTALLURIA IN HEALTHY SUBJECTS. W.J. Maierhofer,* N.D. Adams and J. Lemann, Jr., Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin.

Crystal nucleation must be the initial event in nephrolithiasis. We have reported CaOx or CaP crystals in centrifuged sediments of fasting morning urine maintained at 37°C in 21/30 patients with Ca nephrolithiasis. In these urines, U_{Ca} averaged 9.8± 4.3 SD in comparison to only 4.6±1.8 mmol/L in urines without crystals from 20 normal subjects (p< 0.001). We have now similarly examined sediments from 7 healthy adults before (7 urines) and during (7 urines) oral $CaCO_3$, 2.8 to 4.4 g Ca/day during which $U_{Ca}V$ increased from 4.3±0.6 to 10.3±4.2 mmol/ day (p<0.02) and from 4 healthy subjects before (8 urines) and during (8 urines) oral $1,25-(OH)_2-D_3$, 1 or 2 g/day, during which $U_{Ca}V$ increased from 4.3± 1.8 to 9.9±2.3 mmol/day (p<0.05). CaP crystalluria was produced in 4/7 subjects given $CaCO_3$ and CaOx crystalluria was produced in 2/4 and CaP in 1/4 given $1,25-(OH)_2-D_3$. In 9 urines with crystals, U_{Ca} averaged 7.2±1.6 mmol/L in comparison to only 3.7± 1.7 mmol/L in urines without crystals; p<0.001. U_{Ox} and U_P averaged 0.32±0.11 and 28±11 and 0.26±0.10 and 25±12 mmol/L in urines with and without crystals, respectively; NS. Urines containing CaP tended to be more alkaline (pH 5.9±0.4) than urines without crystals (pH 5.5±0.4) thus increasing estimated $HPO_4^=$ concentrations. These observations reconfirm the importance of U_{Ca}, in addition to U_{Ox}, in determining CaOx crystalluria and U_{Ca}, in addition to U_P and a high urine pH, in determining CaP crystalluria. Examination of the warm urine sediment remains a simple clue to hypercalciuria.

DIFFERENT RESPONSE OF PARATHYROID HORMONE (iPTH) AND DIVALENT CATIONS TO EXPERIMENTALLY-INDUCED METABOLIC ACIDOSIS. J.R. Oster, G.O. Perez, H. Alpert,* J. Canterbury,* and C.A. Vaamonde. V.A. Medical Center and Dept. of Medicine, University of Miami School of Medicine, Miami, Florida.

Because of the differing response of plasma K and P to infusion of mineral versus organic acids we have evaluated the plasma response of divalent cations and iPTH to 3 hr infusion of 0.45% NaCl (control, C), a mineral (HCl) and two organic acids (lactic, LA; methylmalonic, MM) in anesthetized dogs (n=6 in each group). The changes (↑ or ↓) at 3 hr from baseline were:

		C	LA	MM	HCl
pH		0±.02	↓.29±.03†§	↓.28±.02†§	↓.23±.02†§
P	(mg/dl)	↓.1±.3	↑1.8±.4*§	↓.4±.2*†	↑.7±.3
Ca^{++}	(mEq/l)	↓.09±.04	↑.19±.08*†	↑.16±.03*§	↑.12±.02†‡
Mg	(mEq/l)	↓.14±.05*	↓.03±.08	↓.27±.09*	↓.24±.06*
iPTH	(µlEq/ml)	↑ 5±2	↓ 14±12	↑33±7†‡	↑ 20±10
iPTH	(%)	↑ 5±2	↓ 14±15	↑43±10‡	↑28±15

X±SE; * P<0.05; ∓ P<0.005 vs baseline; ‡ P<0.05; § P<0.005 vs C; Ca^{++}=ionized calcium.

Baseline values did not differ. In all groups but LA, Mg decreased. Despite ↑ECF in all and ↑P in LA and HCl, Ca^{++} was increased by all 3 acids. Nevertheless, iPTH increased by 43% after MM and decreased by 14% in LA (P<0.025 MM vs LA). Changes in iPTH were delayed, while those of pH were immediate. Declining plasma Mg in MM and HCl might have offset suppressive effects of increasing Ca^{++} on iPTH. We conclude that in acute metabolic acidosis the anion may have an important modifying effect not only on plasma P and Mg but indirectly (Mg?) or directly influences the response of PTH.

DEMONSTRATION OF A RENAL PHOSPHATE LEAK IN STONE FORMERS WITH HYPOPHOSPHATEMIC ABSORPTIVE HYPERCALCIURIA (HAH). Peña,J.C., Tamayo,J.A.*, Fernández, A*, and Herrera-Acosta,J. Dep. of Nephrology. I.N.N. México 22, D.F., México.

Persistent phosphaturia during phosphate depletion (PD) has been clearly shown in patients with HAH. Six normal controls (N), six patients with HAH and four with normophosphatemic AH (NAH) were studied in 14 day periods. A constant isocaloric diet with 400 mg phosphorus (Pi) and 229 calcium (Ca) was given to all subjects. From day 4 to day 11, 300 ml of aluminum hydroxide (ALOH) was given to insure a complete block of phosphate intake. Urine (U) was collected daily. Blood (B) was drawn on days 3 (C), 6 (D1), 9 (D2) and 12 (E). Ca, Pi and creatinine and immunoreactive parathyroid hormone (iPTH) were measured in all samples. Data are reported as mean ± one standard deviation. A $p<0.05$ is considered significant (*). Phosphorus in U (mg/day) and S (mg/dl) in HAH were compared statistically against normals (upper*) and NAH (lowers*).

	C		D1		D2		E	
Days	U	S	U	S	U	P	U	S
N	526	4.25	26.2	3.45	0	2.64	137	3.7
	46	0.45	12.0	0.44		0.27	56	0.55
NAH	734	3.7	10.5	3.12	0	3.37	153	3.98
	113	0.36	10.5	0.24		0.22	62	0.4
HAH	676	2.52*	93.4*	2.14*	76.4*	2.0	175	2.8*
	76	0.19*	30.5*	0.3*	23.0*	0.27*	64	0.2*

iPTH values were equal in all groups after PD. Tm PO4/GFR was low in HAH. Calciuresis was similar in all groups. The results are compatible with a renal defect to reabsorb Pi not mediated by PTH. The mechanism of this phosphaturia is not yet well characterized.

HEMODIALYSIS OSTEOMALACIA WITH FRACTURES POSSIBLY RELATED TO ALUMINUM INTOXICATION FROM DIALYSATE OR REDY CARTRIDGE. Alkis Pierides, Peter Frohnert, William Johnson, Division of Nephrology, Mayo Clinic, Rochester, Minnesota.

Bordier et al have shown that anephric, $1,25(OH)_2D_3$ deficient hemodialysis (HD) patients do not always develop osteomalacia (OM) while others with severe OM may not improve on treatment with DHT, $1\alpha OHD_3$ or $1,25(OH)_2D_3$ {2}. In rats, parenteral aluminum has been shown to lead to $1,25(OH)_2D_3$, resistant OM {3}.

Over the last four years, 13 HD patients with histologically severe osteomalacia and fractures have been studied. Six dialyzed in a center with a high dialysate aluminum concentration (Al=140µg/L, five developed the syndrome while using the Redy cartridge, and two while dialyzing with apparently deionized water. All patients were receiving aluminum-containing antacids. Trabecular bone aluminum estimated in eight of the patients including the two using deionized water was very high {mean=301, range=180-680 ppm, normal <10 ppm}. Serum calcium and phosphorus were unremarkable and serum PTH was only mildly elevated.

In vitro studies of 6 Redy cartridges have revealed a significant release of aluminum in a form that readily crossed the cuprophan dialysis membrane.

A syndrome of HD osteomalacia exists, unrelated to classical calcium, phosphorus, and vitamin D abnormalities. Aluminum intoxication from dialysate or by release from the Redy cartridge may be responsible for some aspects of this syndrome.

1. Bordier et al: Clin Sci 44, 33-41, 1973
2. Pierides et al: Lancet 1, 1092-1095, 1976
3. Ellis et al: J Clin Path 32, 832-844, 1979

● 1,25-DIHYDROXYCHOLECALCIFEROL(1,25-DHCC):EFFECT ON PHOSPHATE(PO4) ABSORPTION BY ISOLATED PARS RECTA OF RABBIT. R.A.Peraino and W.N.Suki. Baylor College of Medicine, Dept. of Medicine, Houston, Texas.

Vitamin D and its metabolites affect renal PO4 absorption, with and without PTH as a co-factor. Since PTH inhibits PO4 absorption in the isolated pars recta(PR) of the rabbit, we studied the effect of 1,25-DHCC in segments from D and PO4 replete animals. Superficial(SF) and juxtamedullary(JM) PR were bathed and perfused with the same artificial solution simulating plasma but without protein. Four groups were studied. GROUP I:control(C)-1,25-DHCC vehicle;experimental(E)-1,25-DHCC, 10nM. GROUP II:time control without additive. GROUP III:8-bromo cAMP, 10uM, time control. GROUP IV:C-8-bromo-cAMP; E-8-bromo-cAMP + 1,25-DHCC. The concentrations of additives were the same in perfusate and bath. GROUPS I-III showed no changes in lumen to bath PO4 flux(JlbPO4), rate of fluid absorption(Jv) nor potential difference(PD) when the means of C were compared to E within each group. GROUP IV results:

		Jv(nl/min/mm)	JlbPO4(pmol/min/mm)	PD(mV)
SF	C	0.25 ± 0.07	1.47 ± 0.33	-1.1 ± 0.2
n=5	E	0.25 ± 0.06	0.68 ± 0.17	-0.7 ± 0.1
	p	NS	<0.02	NS
JM	C	0.22 ± 0.07	0.76 ± 0.14	-0.8 ± 0.1
n=5	E	0.24 ± 0.06	0.29 ± 0.12	-0.7 ± 0.3
	p	NS	<0.001	NS

Values are mean ± SE. Neither time alone, nor time + cAMP, nor 1,25-DHCC alone affect JlbPO4. 1,25-DHCC in presence of cAMP inhibits JlbPO4 in both SF and JM PR without changes in Jv nor PD. We conclude 1)PO4 is absorbed by an active mechanism. 2) no nephron heterogeneity for JPO4 in PR. 3) 1,25-DHCC with cAMP inhibits PO4 absorption in D replete rabbits, and may be a modulator of cAMP action.

● PARATHYROID HORMONE (PTH) AND PROSTAGLANDIN E2 (PGE2) INTERACTIONS ON PHOSPHATE EXCRETION. J. B. Puschett and J. Fragola,* University of Pittsburgh School of Medicine, Pittsburgh, PA

Previous studies from this laboratory have suggested that not all of the effects of physiological amounts of PTH on the kidney are mediated by the adenylate cyclase system. Furthermore, prostaglandins and PTH can both affect phosphate transport. We therefore evaluated the effects of the infusion of physiological doses (0.3-0.5U/kg/hr) of PTH AND PGE2 (0.5µg/kg/min) on absolute (UPV) and percentage (%EP) phosphate excretion, following the procurement of control data (C), in chronically thyroparathyroidectomized dogs. When PGE2 was superimposed upon PTH infusion, UPV, which had risen from 9.4 ± 3.8 to 17.1 ± 4.3 µmole/min ($P<.025$) after PTH, did not increase further: 18.8 ± 8.4 µmole/min ($P>.60$). Similar findings were obtained for %EP: C: 10.2 ± 4.7%: + PTH: 19.7 ±5.8% ($P<.001$); + PGE2: 21.5 ± 10.7% ($P>.70$). However, when PGE2 was given first, the phosphaturic effect of PTH was blocked: UPV, C: 3.7 ± 1.8; + PGE2: 0.4 ± 0.1 ($P>.10$); + PTH: 1.5 ± 0.9 µmole/min ($P>.20$). For %EP, C: 4.4 ± 1.9%; + PGE2: 0.6 ± 0.2% ($P>.10$); + PTH: 2.3 ± 1.3% ($P>.20$). There were no consistent alterations in renal hemodynamics or in serum ultrafilterable calcium concentration. These data indicate that PGE2 can obviate the phosphaturic effects of PTH. The action of PGE2 could be related to direct membrane effects or to alterations induced by PGE2 in the interaction between PTH and its receptors.

EFFECT OF HYPERCAPNIA AND LUMINAL pH ON PHOSPHATE TRANSPORT IN THE PROXIMAL TUBULE OF THE RAT. Gary A. Quamme and Norman L.M. Wong, Dept. of Medicine, Acute Care Unit, University of British Columbia, Vancouver, British Columbia, Canada.

We have reported that absolute and fractional phosphate reabsorption is greater at luminal alkaline pH than acid and the phosphaturic response of PTH is independent of the luminal pH (Kidney Inter. 16: 832, 1979). Acute hypercapnia is associated with an increase in the urinary excretion of phosphate. To determine the effect of luminal pH in hypercapnia, proximal tubules were perfused in vivo with equilibrated Ringer's solutions buffered with HEPES, pH 7.6 or MES, pH 6.6 equilibrated with 5% CO_2. Buffer (S) and electrolytes were quantitated with electron microprobe and HCO_3^- by microcalorimetry. In normal TPTX rats (Blood pH 7.44, HCO_3^- 21mM/l PCO_2 34 mmHg) fractional reabsorption was greater at luminal pH 7.3 than pH 6.7; 68 ± 4% and 35 ± 4%, n = 27 respectively. The perfused lengths were 2.11 ± 0.11 and 2.72 ± 0.29 mm. Acute hypercapnia was produced by ventilation with 10% CO_2 (Blood pH 7.20, HCO_3^- 29 mM/l, PCO_2 74 mmHg). Overall renal phosphate excretion rose from 0.16 ± 0.10 to 2.7 ± 0.8%. Proximal reabsorption was greater at luminal pH 7.4 than pH 6.7; 61 ± 7% and 35 ± 7% respectively and was similar to that observed in normocapnia however absolute phosphate reabsorption in the alkaline perfusion increased from 1.5 pM/mm/min to 3.6 pM/mm/min. These data demonstrate that phosphate reabsorption is greater at luminal alkaline pH and indicate that acute hypercapnia results in phosphaturia through a change in luminal pH.

URINARY EXCRETION OF 25-OH-VITAMIN D IN HEALTH AND THE NEPHROTIC SYNDROME. K.A. Sato,* R.W. Gray,* N.D. Adams and J. Lemann, Jr. Sponsored by J.D. Beres. Departments of Medicine and Biochemistry, Medical College of Wisconsin, Milwaukee, WI.

Patients with the nephrotic syndrome may have low serum 25-OH-D concentrations, presumed to be the result of urinary losses of vitamin-D-binding protein carrying 25-OH-D. We measured urinary 25-OH-D excretion in 4 normal adults and 6 nephrotics (serum creatinine 1.2±0.4 SD mg/dl, proteinuria 9.2±5.4 g/day and serum albumin 2.5±0.9 g/dl). Twenty-five to 200 ml urine were spiked with 1,800 dpm ^{3}H-25-OH-D_3, incubated with β-glucuronidase, extracted with $CHCl_3$:MeOH and sequentially purified by LH-20, Lipidex and HPLC chromatography. Recovery of spike averaged 60%. 25-OH-D was measured by protein binding assay. Recovery of added unlabelled 25-OH-D ranged from 94 to 100%. Total urinary 25-OH-D excretion in normals ranged from 50 to 192 pmol/day (20 to 76 ng/day) and in nephrotics from 270 to 10,600 pmol/day (109 to 4,240 ng/day). Serum 25-OH-D in normals and nephrotics averaged 89±15 and 30±10 nmol/L, respectively; $p<0.01$. Estimated clearance of 25-OH-D was directly related to the estimated clearance of albumin. Endogenous 25-OH-D production in health was previously estimated from the plasma disappearance of injected ^{3}H-25-OH-D_3 and averaged about 7,000 pmol/day (2,800 ng/day) with less than 1% appearing as ^{3}H-25-OH-D_3 in urine. The present measurements of urinary 25-OH-D excretion in normals are consistent with those results. The large urinary losses of 25-OH-D in some nephrotics clearly exceed normal production rates and may result in vitamin D deficiency in the absence of compensatory increases in sun exposure or dietary vitamin D intake.

CALCIUM INFUSION IN RENAL TRANSPLANT PATIENTS (RTP). EFFECTS ON SERUM PARATHYROID HORMONE (iPTH), URINARY cAMP EXCRETION ($U_{cAMP}V$), AND ALLOGRAFT HANDLING OF INORGANIC PHOSPHATE (Pi). A.J. Rivero, R.C. Pabico, B.A. McKenna, W.E. Hoy. Nephrology Unit, Univ. of Rochester Med. Center, Rochester, N.Y.

Elevated iPTH in RTP persists even beyond 12 months after transplantation, and good allograft function. To assess the suppressibility of the parathyroid glands, IV calcium infusions (14 mg/Kg in 3 hours) were performed on 5 RTP (14 months post-transplant with normal allograft function) with the patients in the post-absorptive state undergoing water diuresis. This study also defines the effects of hypercalcemia on allograft hemodynamic functions and Pi metabolism in RTP. Serum total calcium (Tca), Ca^{++}, Mg^{++}, Pi and iPTH, $U_{cAMP}V$, tubular reabsorption of Pi (Tm_{pi}/GFR), GFR and ERPF were measured before, during and after IV calcium. Tca increased from 10.4 to 14.8 mg/dl, and Ca^{++} rose from 2.58 to 3.84 mEq/L following IV calcium. There was no change in Mg^{++}. The effects on the various functions (mean ± 1 SE) are as follows:

	Pre-infusion	Post	p
iPTH (pg/ml)+	5984±1688	3122±932	**
$U_{cAMP}V$ (nm/100 ml GFR)	5.18± .64	2.57±.23	**
Serum Pi (mg/dl)	2.02± .08	4.08±.36	**
Tm_{pi}/GFR (mg/100 ml)	0.93± .21	2.50±.32	**
GFR (ml/min/1.73 m^2)	69± 5	65± 4	*
ERPF "	274± 36	253± 31	*

+ normal = ≤ 2000; ** << .001 * < .05

We conclude a) that PTH secretion in RTP is partially suppressed by hypercalcemia and is reflected in decline in $U_{cAMP}V$ and increase in Tm_{pi}/GFR, b) that the changes in Tm_{pi} and serum Pi persist longer than iPTH inhibition indicating that hypercalcemia directly influences allograft Pi handling.

● EXTRACTION OF VITAMIN D METABOLITES BY THE ISOLATED PERFUSED BONE OF NORMAL DOGS. J. Schwartz,* K. Olgaard, D. Finco, K. Martin, J. Haddad, L. Avioli, S. Klahr, E. Slatopolsky. Renal and Bone Mineral Div., Washington Univ., St. Louis, MO.

The role of the skeleton in the metabolism of vitamin D is poorly defined. To further characterize the skeletal handling of different metabolites of vitamin D: 25(OH)D_3, 24,25(OH)$_2D_3$ and 1,25(OH)$_2D_3$, we examined the A-V extraction of these compounds by the isolated perfused tibia from normal dogs. The nutrient artery to the tibia was cannulated and perfused with Krebs-Henseleit buffer. After equilibration, the venous effluent was collected for 16 x 5 minute periods. The specificity of the extraction was verified by minimal (1-8%) A-V differences for ^{3}H-Cholesterol, ^{3}H-Aldosterone and ^{14}C-Inulin. The extraction of ^{3}H-25(OH)D_3 averaged 50% (range: 30-65%). When ^{3}H-25(OH)D_3 was preincubated with 25, 100 or 500µl dog serum (containing vit. D binding protein-DBP) the uptake decreased to 32, 10 and 5% respectively. Extraction of 24,25(OH)$_2D_3$ averaged 35% and decreased during addition of small amounts of serum (DBP). By contrast the extraction of 1,25-(OH)$_2D_3$ (30%) did not change when DBP was added. In the venous effluent no metabolites of 25(OH)D_3 were demonstrable. The extraction of ^{125}I-hDBP was negligable. In conclusion, a significant amount of free metabolites of vit. D are extracted by adult dog bone. These data suggest a storage function of DBP in vivo, which limits the delivery of free 25(OH)D_3 and 24,25(OH)$_2D_3$ to their target tissues while the handling of 1,25(OH)$_2D_3$ is unaltered by the presence of DBP. This model should permit a detailed study of the handling of vitamin D by bone in uremia.

● TWO CALCIUM TRANSPORT SYSTEMS IN TOAD BLADDER: ACTIVATION BY CYCLIC NUCLEOTIDES AND PROSTAGLANDIN. B.B. Sellers, Jr. and B.G. Gray*. Med. College of Ga., Augusta, Georgia.

We have previously shown that parathyroid hormone (PTH) increases Ca transport across the toad urinary bladder (Sellers, et al Kidney Int. 16:837, 1979). Further studies were performed to evaluate the effects of dibutyryl cyclic AMP(dcAMP) dibutyryl cyclic GMP(dcGMP) and prostaglandin E_2 (PGE_2) on toad bladder Ca transport. Isotopic flux of ^{45}Ca was studied in the toad bladder in a modified Ussing chamber under short-circuit conditions. Mucosal-to-serosal (M→S) Ca flux(Jca) and serosal-to-mucosal(S→M) Jca were studied in separate pieces of the same hemibladder. Jca was measured for a one hour control period initially. Following the control period, dcAMP (0.04mM/L), dcGMP (1.0mM/L), PGE_2 (0.05μg/ml), or PGE_2+dcAMP were added to the serosal bathing soln. 15 minutes later, a one hour flux period began and Jca was measured. Results are reported as the mean±SE of the fractional increase in Jca (FIJca) calculated as (Jca exper.-Jca control/Jca control). n=number of bladders. †=P<0.05.

		dcAMP	dcGMP	PGE_2	dcAMP+PGE_2
FIJca	M→S	†1.1±0.4	0.0±0.1	0.0±0.2	†1.0±0.4
	S→M	0.1±0.2	†1.0±0.4	†0.8±0.3	†1.5±0.4
		n=8	n=9	n=10	n=7

From the above data we conclude that there are two Ca transport mechanisms: 1) M→S Ca transport mechanism which is activated by PTH and dcAMP; 2) S→M Ca transport mechanism which is activated by dcGMP and PGE_2. These two Ca transport mechanisms seem to be activated independently but can operate simultaneously.

● PHOSPHATE (Pi) TRANSPORT IN CHRONICALLY DENERVATED RAT KIDNEYS. L.Szalay*, R.E.Colindres, R.Jackson*, J,T, Adkinson*, W.E. Lassiter, C.W. Gottschalk, Dept. Med., Univ. North Carolina, Chapel Hill, NC.

Salt, water and phosphate transport were evaluated in the proximal tubule and loop of Henle of 9 anesthetized rats with chronic denervation of left kidney (DEN) and 9 sham denervated rats (C) during sustained ECF volume expansion (5% body weight).

All denervated kidneys showed a significant diuresis and natriuresis in comparison to the right kidney and to the sham denervated kidney of C rats. C_{In} and C_{PAH} were similar in both kidneys and in both experimental groups. Fractional excretion of Pi was greater from the denervated than from the sham denervated kidneys (33.5±4.4% SE and 18.3± 2.0%, P<0.01**). Single nephron GFR and F/P In ratios in early proximal (EP), late proximal (LP) and early distal convolutions (ED)were similar in the DEN and C groups. F/P Pi and percent filtered Pi remaining in each nephron segment (FD_{Pi}%) were as follows:

		ED	LP	EP
$\frac{F}{P}_{Pi}$	C	1.48±0.25	0.93±0.03	0.95±0.05
	DEN	2.01±0.12	1.22±0.04**	1.05±0.02
FD_{Pi}%	C	32.2±4.6	52.5±2.7	77.2±2.9
	DEN	52.3±3.3**	72.2±3.0**	88.6±1.7**

We conclude: a) Chronic denervation produced decreased Pi reabsorption in the proximal tubule without associated changes in Na or water reabsorption. b) The inhibition is observable in the earliest segment of the proximal tubule accessible for micropuncture. c) The observed diuresis and natriuresis must result from inhibition of Na and water reabsorption beyond the proximal convolution or in deep nephrons.

● HYPOPHOSPHATEMIA WITHOUT PRIOR PHOSPHATE DEPLETION: EFFECT ON RENAL FUNCTION. Thomas H. Steele, Laura Challoner-Hue,* and Jeanne H. Gottstein,* University of Wisconsin, Madison, Wisconsin.

Phosphate (P) depletion results in renal Ca and Mg wastage and increased capacity for P reabsorption in the isolated perfused rat kidney (Kidney Int. 13:124, 1978). To determine if hypophosphatemia (HP) affects renal function similarly to P depletion, we perfused isolated kidneys from normal rats with synthetic P-free perfusate for 1 hour. GFR was normal in all HP kidneys, but absolute and fractional excretion (FE) of Na and Ca were increased over controls in half (FENa 18 ± 5% in HP and 1.9 ± .4% in controls, P < 0.001; FECa 19 ± 6% in HP and 4.8 ± 1.2% in controls, P < 0.01). In the remainder, FENa and FECa were normal during HP. Maximum P reabsorption during acute perfusate P elevation was 104 ± 4 μg/ml GFR in controls, 99 ± 12 in normally functioning HP, and 62 ± 11 in natriuretic hypercalciuric HP kidneys (P < 0.001). In contrast, FEMg averaged 25 ± 5% and 32 ± 6% in the 2 HP groups, irrespective of FENa and FECa, as compared to FEMg of 11 ± 2% in controls (P < 0.01). P loading did not decrease FECa or FEMg in either HP group.

HP does not result in enhanced P reabsorptive capacity or in hypercalciuria without Na wastage, but may account for renal Mg wastage in P depletion. HP also predisposes to the development of renal tubule dysfunction.

● THE EFFECTS OF PHOSPHOCITRATE ON EXPERIMENTALLY INDUCED NEPHROCALCINOSIS. W.P. Tew,* C.D. Malis,* and W.G. Walker. The Johns Hopkins Hospital, Baltimore, Maryland.

The progressive renal destruction from nephrocalcinosis (NC) of hyperparathyroidism, vitamin D intoxication, milk-alkali syndrome and related disorders justifies a search for substances that will prevent and possibly reverse such calcification. We have synthesized phosphocitrate and documented its powerful inhibitory effects upon crystallization of calcium phosphate salts (Tew, et al, Biochem. 19:1983-1988, 1980).

Mice receiving 50 U parathormone daily intraperitoneally (ip) develop NC within 4 days and Ca++ increases from 2.1±.4 (SEM) μmol/gm kidney to 59.5±6.4 μM/gm kidney. Mice similarly treated but receiving 1.0 μmol phosphocitrate ip before each PTH injection only increased calciums in renal tissue to 10.5±2.4 μmol/gm on day 4 (p<.001). Equally significant reductions in renal Ca++ were observed with as little as 0.075 μmol of phosphocitrate/day. Reduction in tissue Ca++ occurred without change in the PTH induced hypercalcemia. Calcium gluconate-induced NC in rats was also inhibited by phosphocitrate with Ca++ decreasing from 125±17 μM/gm kidney in gluconate treated group to 36.5±7 μM/gm in the gluconate and phosphocitrate group (p<.003), also without reducing the hypercalcemia. Thus phosphocitrate may function at the cell level to inhibit crystallization of calcium salts despite a persistently high calcium x phosphate product in the extracellular fluid and hence may be therapeutically important in preventing nephrocalcinosis in clinical situations.

EFFECTS OF FUROSEMIDE AND HYDROCHLOROTHIAZIDE ON RENAL TUBULAR TRANSPORT IN FAMILIAL HYPOCALCIURIC HYPERPARATHYROIDISM (FHH). H. Watanabe,* Univ. of Alberta, Calgary and R.A.L. Sutton, Dept. of Med., Univ. of British Columbia, Vancouver, Canada.

We have examined the responses to single oral doses of hydrochlorothiazide (100 mg) and furosemide (60 mg) in 2 members of an FHH kinship and in 4 patients with primary parathyroid adenoma or hyperplasia (HPT). Following an overnight fast, urine samples were collected from 7-9 am, the drug was given at 9 am and urine was again collected during continued fasting from 9am -1pm. In HPT, the mean urinary Ca/Na ratio (mgCa/mEq Na) before diuretic administration was 2.78 compared with 1.22 in FHH, confirming the presence of relative hypocalciuria in the FHH patients. After hydrochlorothiazide the mean Ca/Na ratio fell to 0.80 in HPT and to 0.43 in FHH, as a result of increases in Na excretion with little change in Ca excretion in both groups. After furosemide, the mean Ca/Na ratio was 1.00 in HPT and 0.99 in FHH. Thus the characteristic dissociation of tubular Na & Ca transport in FHH persists after hydrochlorothiazide but is abolished by furosemide. Since furosemide inhibits the transport of Na & Ca in the thick ascending limb of Henle's loop, these data suggest that the augmented calcium reabsorption in FHH may be occurring at this site, perhaps as a result of increased permeability to the passage of calcium ions. Furosemide, by inhibiting chloride transport, abolishes the driving force for calcium absorption and would therefore mask such an abnormality.

ALTERED PARATHYROID HORMONE (PTH) SENSITIVITY OF THE UREMIC PROXIMAL TUBULE: EVIDENCE FOR REGULATION OF HORMONE-RECEPTOR INTERACTION. Norimoto Yanagawa*, Barbara Houston*, and Leon G. Fine. Division of Nephrology, Center for the Health Sciences, UCLA School of Medicine, Los Angeles, CA.

In vivo studies on animals with experimental chronic renal failure have shown that the phosphaturic response to both endogenous (Kidney Int 14: 207, 1978) and exogenous PTH (Metab 27:1785, 1978) is enhanced in uremia. This response is greatest in uremic animals maintained in a euparathyroid state by dietary phosphorus restriction. The present study examined the *in vitro* PTH response of the isolated perfused proximal straight tubule (PST) from normal (N), hyperparathyroid-uremic (U-HP), and euparathyroid-uremic (U-NP) rabbits. A dose-response relationship between bath concentration of (1-34)bPTH and inhibition of lumen-to-bath phosphate flux $J_p(lb)$ (pmol/mm/min) was determined. Half-maximal inhibition of $J_p(lb)$ occurred at a bath PTH concentration of 5×10^{-3} units/ml in normal PSTs, at 5×10^{-4} units/ml in U-NP tubules, and at 5×10^{-2} units/ml in U-HP tubules. Maximal bath concentrations of PTH inhibited $J_p(lb)$ by approximately 30% in all three groups. Mean basal $J_p(lb)$ was 5.17 in N, 7.66 in U-HP, and 10.51 in U-NP. Thus, the absolute reduction in $J_p(lb)$ was greater in both uremic groups than in N. Conclusions: 1. PSTs from uremic rabbits have an altered response to PTH. 2. The response is blunted in U-HP tubules and is enhanced in U-NP tubules. 3. The different response of U-HP versus U-NP tubules suggests that PTH receptors are "down-regulated" in the HP state and show increased sensitivity when the secondary hyperparathyroidism of uremia is prevented.

Clinical Nephrology

INTRAPERICARDIAL STEROID TREATMENT FOR UREMIC PERICARDITIS AND PERICARDIAL TAMPONADE. R.D. Almkuist, J.W. Snyder,* W.P. Nixon, Wilmington, North Carolina.

Percutaneous pericardial catheterization and intrapericardial steroid injection (PPCISI) was used to treat uremic pericarditis and pericardial tamponade in eight ESRD patients over a four year period. All patients had failed to respond to increased hemodialysis and non-steroid anti-inflammatory agents. Pericardial catheterization was performed using a subxiphoid approach with the patient's head elevated. An 18 gauge thin wall needle was advanced until pericardial fluid was easily aspirated. A "J" shaped flexible guide wire was inserted through the needle. The needle was removed and a #7 French angiographic catheter was inserted over the guide wire. Fluoroscopy was used in seven of eight patients. In each patient pericardial fluid was aspirated and air and triamcinolone hexacetenide were injected (average single dose 70.5 mgm, range 40-100 mgm: average total dose 167.5 mgm, range 80-230 mg.). The catheter was left in place and aspirations and injections were repeated usually 2 to 3 times over a 48 hour period. All patients responded promptly. There have been no complications. One patient died at two months of a cerebral infarction. The remaining seven patients are alive and have had no evidence of recurrence in 63 months of patient follow-up (average 9 months per patient, range 1-27 months). PPCISI is a safe and effective treatment for uremic pericarditis and pericardial tamponade.

CLINICAL TRIAL OF CYCLOPHOSPHAMIDE PLUS AZATHIOPRINE AND PULSE CYCLOPHOSPHAMIDE IN LUPUS NEPHRITIS. JE Balow, HJ Dinant*, JL Decker*, JH Klippel*, PH Plotz* and AD Steinberg*. Arthritis & Rheumatism Branch, NIAMDD, NIH, Bethesda, Maryland.

In a randomized, prospective study, 41 patients with active lupus nephritis were allocated to the following treatment groups: 1) Conventional high-dose oral prednisone (PO), 2) Combined low-dose (0.5mg/kg/day) oral prednisone plus cyclophosphamide and azathioprine (CA) or 3) Low-dose prednisone plus pulses of intravenous cyclophosphamide (IC) every 3 mos. The renal outcomes of 39 patients followed for ≥ 1 year (mean 42 mo) were:

Group	n	Renal Failure	Worsened Creatinine	Hypertension
1. PO	12	0	4 (33%)	10 (83%)
2. CA	16	0	2 (13%)	9 (56%)
3. IC	11	0	1 (9%)	11 (100%)

There were no significant differences in rates of change of hematuria, proteinuria, DNA binding or C3 levels among treatment groups.

Complications observed during followup were:

Group	Death	Major Infec	Herpes Zoster	Ovarian Failure	Avascular Necrosis
1. PO	1 (P.E.)	1	0	2/11	6
2. CA	1 (CVA)	2	3	5/14	2
3. IC	2 (CAD,Inf)	2	2	3/9	1

Hemorrhagic cystitis and prolonged bone marrow depression each occurred once in the CA group. No malignancies have occurred in this study. Although differences in renal function did not reach statistical significance, the trend toward more favorable renal outcomes and the reduced incidence of serious bone complications in patients treated with cytotoxic agents may indicate an advantage of these drugs during longer followup studies.

HYPERKALEMIC HYPERCHLOREMIC METABOLIC ACIDOSIS (MA) IN PATIENTS WITH SICKLE CELL HEMOGLOBIN. D.C. Batlle, K. Itsarayoungyen,* J.A.L. Arruda and N.A. Kurtzman. Univ. of ILL., Chicago, ILL.

Impaired ability for K secretion has been demonstrated in patients with hemoglobin S and normal GFR. Hyperkalemia, however, has not been documented. Four patients with SS, SC and SA (2) hemoglobinopathies repeatedly presented with unexplained hyperkalemic hyperchloremic MA (plasma K 6.6±0.5 mEq/L, Cl 113±1.7 mEq/L, blood pH 7.28±0.01, plasma HCO_3^- 18±0.8 mEq/L and blood pCO_2 35±4.0 mmHg) and moderately reduced GFR (45.7±8.3 ml/min). All patients had depressed baseline K excretion as demonstrated by a value of fractional K excretion (FEK) lower than controls with comparable GFR (FEK 12±1.7% and 39±2.0%, $p<0.001$ respectively). The capacity for K secretion and distal acidification was investigated by the administration of mineralocorticoid and Na_2SO_4 in 3 patients. The two SA patients failed to increase FEK normally in response to this maneuver. The SC patient responded to Na_2SO_4 with a normal increase in FEK and a fall in UpH below 5.5. Impaired Na conservation was demonstrated in one of the SA patients who was the only one studied on a 10 mEq/Na diet. Our findings can be best explained on the basis of a primary impairment of distal Na transport which prevents the generation of a favorable electrical gradient for both K and H^+ secretion (voltage dependent distal renal tubular acidosis). Mild defects in Na transport (i.e. our SC patient) may be responsive to enhanced distal Na transport with $NaSO_4$ whereas more severe defects (i.e. our 2 SA patients) may not be responsive. S hemoglobinopathies should be considered in the differential diagnosis of hyperkalemic hyperchloremic MA.

ENZYMURIA (E) CAN PREDICT OUTCOME OF ISCHEMIC ACUTE RENAL FAILURE (IARF). Camilo G. Barcenas, Alan Rogers*, Denton Cooley*, Layne Gentry*, St. Luke's Hospital, Texas Heart Institute, and Baylor College of Medicine, Houston, Texas.

Although E has been used to diagnose acute rejection and drug nephrotoxicity, its value in IARF hasn't been determined.

Patients with oliguric (O), non-oliguric (NO), at high risk (HR) of IARF and normal post-operative (NPO) were studied. Creatinine clearance (CCr), FENa, urine to plasma osmolarity (U/PO), N-acetyl Beta-glycosidase (NABG), alanine aminopeptidase (AAP) were measured enzymatically at consultation (C), and/or post-operatively (NPO) and sequentially to dialysis, death or recovery. Results at C (means ±SEM):

	n	CCr ml/min	FENa%	U/PO	NABG*	AAP*	
NPO	10	61± 9	1.3 ±0.3	1.8 ± 2	0.9 ±0.2	0.3 ±0.1	
HR	11	29±11	7.2 ± 3	1.7 ±.2	5.4 ±2.4	7 ± 3	+
NO	7	9 ±2	2.7 ± 1	1.1 ±.1	5.3 ±1.6	5.5 ± 1	+
O	12	8 ±3	1.7 ±0.5	1.0 ±.1	12.5± 4	44 ± 12	++

* Units/hr/mgCr + $p<0.05$ ++ $p<0.02$

Patients with higher levels of AAP at C, eventually became anuric irrespective of initial urine volume, GFR, FENa, U/PO or UpCr. Two patients with NO became O following protracted insults with concomitant increase in E. In HR, E lasted a few hours post-operatively then resolved to NPO levels.

Furosemide failed to induce a diuresis in O, but patients with NO responded. This correlated with AAP. No correlation of E was found with tubular dysfunction.

Conclusions: The level of E correlates with the severity of IARF, has predictive value for outcome, and can be very useful in the clinical management of patients.

BASAL GANGLIA CALCIFICATION AND SYMPTOMATIC HYPERNATREMIA ASSOCIATED WITH THE SYNDROME OF INAPPROPRIATE ANTIDIURETIC (SIADH) SECRETION. D. Bichet,* G. Lum, W. Handelman,* and R. Schrier. Dept. Med., Univ. Colo. Hlth. Sci. Ctr., Denver, CO.

A 15 year old obese boy presented with a grand mal seizure and a plasma sodium concentration (PNa) of 170 mEq/L. Osmotic regulation of arginine vasopressin (AVP) was totally abolished as hypertonic (3%) saline increased neither urine osmolality in mOsm/kg H_2O (Uosm, 468 to 330) nor plasma AVP (2.0 to 0.5 pg/ml) and water loading (20 ml/kg) suppressed neither Uosm (555 to 506) nor plasma AVP (1.9 to 4.6 pg/ml). Adrenal, thyroid, cardiac and liver function was normal and the patient was not ingesting any drug. Thus, except for the absence of hyponatremia, the patient fulfilled the criteria for SIADH. Two sequential 20 ml/kg water loads over 3 hours further supported this diagnosis as PNa fell to 128 mEq/L with Uosm only decreasing to 204. The explanation for the hypernatremia with SIADH was the virtual absence of thirst perception in this patient. Hypothalamic disease was further documented by hypogonadotrophic hypogonadism, hyperprolactinemia and non-stimulatable growth hormone with insulin or L-Dopa. Lastly, nonosmotic regulation of AVP was tested: neither neck immersion nor 2 liters of saline over 3 hours led to a water diuresis but tilting at 75° for 30 minutes increased Uosm (605 to 838). Computerized axial tomography demonstrated basal ganglia calcifications but no anatomical abnormality of the hypothalamus. A syndrome has thus been described with hypernatremia, adipsia, SIADH, hyperprolactinemia, hypogonadism, and basal ganglia calcifications.

RADIOGRAPHIC CONTRAST MEDIA RELATED ACUTE RENAL FAILURE - A RETROSPECTIVE ANALYSIS. Martin H. Bierman, Michael D. Hammeke, and J.D. Egan. Creighton University School of Medicine, Dept. of Medicine, Omaha, Nebraska.

A retrospective study of consultations for acute renal failure (ARF) revealed 19 cases of radiographic contrast media ARF occurring during a 4 year period. The patients were generally elderly with a mean age of 68 years. Pre-existing disease states included: hypertension (68%), chronic renal insufficiency (53%), proteinuria (63%), heart disease (32%), vascular disease (26%) and diabetes (26%). Routine bowel preparation prior to abdominal contrast studies was used, however no patient was overtly dehydrated at the time of study. A solution containing meglumine diatrizoate was the usual contrast agent. Mean values for urinary indices at the time of diagnosis of ARF were: urine osmolarity 336 mosmol/L., urine sodium 46 mEq/L., fractional excretion sodium 5.4%, urine/plasma (U/P) urea 5, and U/P creatinine 13.6. Mean BUN and creatinine values prior to the contrast study were 30 mg% and 2.2 mg% respectively; mean peak BUN and creatinine values after the contrast agents were 90 mg% and 8.0 mg% ($p < .005$). Oliguria was present in 9/19 patients (47%) with a mean duration of 5.9 days; dialysis was required in 5/19 patients (26%) A mean of 17 days was required for renal function to return to baseline, however 4 patients died following the development of ARF. It is concluded that radiographic contrast media related ARF is not uncommon, occurs in elderly patients with underlying renal or vascular disease, and follows a course similar to ARF from other causes.

SERUM PHENYTOIN CONCENTRATIONS IN UREMIA. A. Blair,* E. Burgess,* P. Friel,* and V. Raisys * (intr. by H. Tenckhoff). Department of Medicine, University of Washington, Seattle, WA.

To compare the enzyme-multiplied immunoassay (EMIT) and gas liquid chromatography (GLC) techniques of assaying serum phenytoin concentrations, 7 normal subjects, 2 subjects with renal insufficiency (creat. clearance 15-28 ml/min/M^2), and 16 hemodialysis patients were studied. One to three blood samples were drawn from each subject, including pre- and postdialysis samples. Each sample was assayed by both EMIT and GLC. In subjects with normal renal function, the serum phenytoin concentrations determined by EMIT and GLC were not statistically different. In patients with renal insufficiency, the EMIT assay determinations were 40% higher ($p < 0.001$) than the GLC determinations, and in hemodialysis patients the EMIT determinations were 90% higher ($p < 0.001$) than the GLC determinations. There was no significant difference between the pre- and postdialysis samples. The source of error does not appear to be the major metabolite, since the degree of error does not correlate to the conjugated or unconjugated 5-para-hydroxyphenyl-5-phenylhydantoin. The widely used EMIT assay gives falsely high results and causes patients with decreased renal function to receive too low a dosage of phenytoin, which results in inadequate anticonvulsant protection.

SKELETAL MUSCLE ION COMPOSITION AND MEMBRANE POTENTIAL IN TYPE IV RTA. Jon D. Blachley, Charles H.Laney† and James P. Knochel. Univ.of Texas Southwestern Med Sch. and Dallas VAMC. Dallas, Tx.

Skeletal muscle is the major repository for body potassium. We attempted to determine if the serum ion composition in hyperkalemic, hyperchloremic metabolic acidosis (type IV RTA) reflects impaired ion transport in skeletal muscle. Resting muscle membrane potential (Em), serum and muscle electrolytes were measured in four males with stable, chronic renal insufficiency and type IV RTA. Control measurements were made with the patients on no medication, and then repeated after two weeks of oral sodium citrate treatment. Serum and muscle electrolytes are shown below. Values are mean +sem.

	Control	After treatment	
serum Na	141.±0.8	141.±0.7	
K	5.7 ±0.2	4.5 ±0.4	*
HCO_3	18.8±1.3	23.3±1.4	*
muscle Na	19.4±2.7	16.4±1.6	**
K	40.1±1.9	41.8±0.7	
Cl	16.3±4.1	8.2 ±1.7	*

[serum values are meq/L, muscle values are meq/dgm fat-free dry weight,*$p<0.05$, ** $p<0.10$.]

Control muscle Em was -92.6±1.8 mv. This rose to -100.5±1.1 mv after treatment ($p<0.05$). Body weight and serum creatinine did not change. These results indicate that muscle, as well as renal K transport may be impaired in type IV RTA. Correction of acidosis and hyperkalemia appears to have enhanced muscle Na-K transport as demonstrated by a decrease in muscle Na and Cl, and an increase in resting muscle Em.

PULSE METHYLPREDNISOLONE THERAPY (Rx) OF IDIOPATHIC ACUTE CRESCENTIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (AC-RPGN) W.K. Bolton, Charlottesville Collaborative Study, Charlottesville, Va.

Thirty patients (pts) with idiopathic AC-RPGN were diagnosed (Dx) since 1974. The clinical Dx excluded systemic diseases and all specimen were examined by light, electron (EM), and immunofluorescence (IF) microscopy. Eighteen were Rx with pulse methylprednisolone 30 mg/kg daily or every other day for three doses and then placed on a protocol of tapering oral prednisone. Untreated pts did not receive pulse. Rx was considered a failure if a pt required and remained on hemodialysis (HD) or died. Pts are divided into histologic categories by IF and EM as (a) anti-GBM (b) immune-complex (IC) or (c) non-immunoglobulin deposit-(NID) types of AC-RPGN.

Dx	Pulse		Non-Pulse	
	Improved/ Total	Off-HD/ HD	Improved/ Total	Off-HD/ HD
Anti-GBM	1/7	0/5	0/5	0/5
IC	4/5	2/3	1/5	0/4
NID	5/6	4/5	1/2	0/1

Thirteen of 18 pulsed and 10/12 non-pulsed pts required HD. Nine of the 11 IC-NID pts showed improvement with pulse Rx compared to 2 of 7 without pulse Rx ($p<.05$). Six of 8 IC-NID pts on HD were able to stop HD after pulse Rx compared to 0/5 non-pulsed pts, $p<.05$. One of 7 anti-GBM pulsed pts improved but none was able to stop HD, not different from non-pulsed pts.

This study shows that pulse Rx of anti-GBM type of AC-RPGN may be of limited value. However, pulse Rx of IC and NID types of AC-RPGN appears to offer significant advantages compared to other types of Rx.

CHRONIC HYPERKALEMIA IN SIBLINGS ASSOCIATED WITH ENHANCED RENAL CHLORIDE ABSORPTION. Emmanuel L. Bravo*, Stephen C. Textor*, Salim Mujais*, and Daniel Cotton*: (Intr. by D. Vidt). Research Division, Cleveland Clinic Foundation, Cleveland, Ohio.

Two healthy adult brothers were evaluated for unexplained hyperkalemia. Both had normal GFR, hyperchloremia, hypertension, low plasma renin activity (PRA) and normal plasma aldosterone (PA). Salt deprivation increased PRA (0.2 and 0.8 to 3.0 and 4.3 ng/ml/hr) and PA (13.5 and 15.6 to 41 and 49 ng/dl) appropriately. Renal concentrating and diluting capacity and urinary acidification following oral NH_4Cl were normal. K^+ clearance fell 30-50% during NH_4Cl loading despite marked increase in serum K^+. Normal potassium (K^+) handling following Na_2SO_4, Furosemide and Florinef (Table) suggests no primary K^+ secretory defect. However, during NaCl infusion, K^+ clearance fell and Cl^- clearance was abnormally low. Florinef corrected K^+ without affecting serum Cl^-.

	(Pt.A) Pre	Post	Pre	Post (Pt.B)
NaCl iv: K^+ (mEq/L)	5.2	5.8	5.3	5.6
: U_kV (μEq/min)	80	56(-29%)	103	91(-11%)
NH_4Cl po: K^+	5.4	6.6	5.0	6.2
: U_kV	77	40(-40%)	54	37(-31%)
$NaSo_4$ iv: K^+	5.5	5.4	5.5	4.7
: U_kV	48	120(+152%)	61	159(160%)
Florinef: K^+	5.8	4.9	5.7	4.6
(0.2 ng/d): Cl^-	109	108	112	111

Serum K^+ fell normally during glucose and insulin infusion suggesting no defect in transmembrane K^+ transfer. In light of normal K^+ secretory mechanisms, we propose that hyperkalemia in these patients is due to enhanced renal tubular reabsorption of chloride.

NETILMICIN (NET) IN PERSISTENT URINARY TRACT INFECTION. Felix P. Brunner,* Gilbert Thiel,* Markus Wenk,* and Ferenc Follath* (intr. by Floyd C. Rector, Jr.). Dept. of Med., Univ. of Basel, Basel, Switzerland.

NET was studied in 9 patients whose urinary tract infection could not be cured by cotrimoxazole, aminopenicillins or other antibiotics. 3 or 2 mg/Kg NET were given i.m. every 24-96 h (a total of 12 to 6 injections during 3 weeks) depending on renal function. NET in serum and urine was measured by radioenzymatic assay. Peak serum NET was 10.6 ± 2.1 and 8.2 ± 1.2 μg/ml (x ± SD) with 3 and 2 mg/Kg resp. Trough level rarely exceeded 1 μg/ml. During treatment urine NET always exceeded 4 μg/ml in patients who were not drinking excessively or receiving furosemide. Independent of renal function, urinary NET/mM creat. decreased with a $t_{1/2}$ of 7 to 10 days from week 2 to 4 after the last dose of NET and more slowly thereafter resulting in urinary NET of 2.8 ± 1.5 μg/ml after 1 and 0.6 ± 0.3 μg/ml after 4 weeks. NET cleared infection (follow-up ≥12 weeks) in 1 of 3 pyelon., 3 of 4 analgesic nephropathies and 2 of 2 renal transplants. Despite prolonged urinary NET excretion, NET-susceptible bacteruria relapsed at 3 to 4 weeks in 2 (1 staghorn calculus) and at 12 weeks in 1 patient (renal abscess). Tenacious urinary infection may be cured with NET using dosage intervals of 24 to 72 h even in patients with normal renal function.

RENAL TUBULAR ACIDOSIS, MARBLE BONE DISEASE AND MENTAL SUBNORMALITY--A SYNDROME. Harold Bregman*, Judith Brown*, Ann Rogers*, Edmund Bourke, Renal-Electrolyte Division and Dept. of Pediatrics, Allegheny General Hosp., Pittsburgh, Pennsylvania.

Osteopetrosis is rarely associated with renal tubular acidosis (RTA) (10 case reports) and we report 3 additional cases including 2 siblings, all of whom demonstrated delayed mental development.

Heterogeneity of the renal acidification defect was the most striking feature. In the siblings, minimum urine pH of 6.3 followed oral ammonium chloride (NH_4Cl) loading. Although ammonium excretion rose substantially, there was no significant increase in urinary titratable acid. Bicarbonate Tm was normal at 27.0 and 26.3 mmol/L, thus indicating Type I (distal) RTA. The third patient similarly failed to lower urine pH below 6.3 following NH_4Cl loading, despite a plasma bicarbonate of 11.5 mmol/L associated with negligible bicarbonaturia. In contrast to the siblings, however, bicarbonate Tm was significantly reduced (18.8 mmol/L), indicating combined proximal and distal RTA. Proximal tubular function was otherwise normal.

Although their benign course was characteristic of the dominant forum of osteopetrosis, the absence of disease in parents and the finding of consanquinity in the third case suggest a recessive mode of inheritance. Osteopetrosis, RTA, and mild mental retardation thus represents a distinct syndrome.

MÉGADOSE METHYLPREDNISOLONE VERSUS PLASMAPHERESIS IN TREATMENT OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN). Frank J. Bruns, Donald S. Fraley, Sheldon Adler, and David P. Segel. Dept. of Med., Montefiore Hospital and University of Pittsburgh Sch. Med., Pittsburgh, PA.

Renal function and complications were followed in consecutive patients with RPGN treated with one of two therapies and followed for at least one year. Biopsy of each patient showed diffuse proliferative GN with epithelial cell crescents. Group I patients treated between 1976-1978 received 1-9 plasma exchanges while group II patients treated in 1979-1980 received 4-11 pulses of methylprednisolone, 30 mg/kg on alternate days. All patients received similar dose daily prednisone 40-120 mg qd and cyclophosphamide 600 mg po q 2 wks for 3-7 months. Plasma creatinine fell from 6.3 to 2.2 mg/dl ($p < .001$) in group I and from 6.5 to 3.7 mg/dl in group II patients ($p < .001$) in the first 3 months. The table shows the number of patients surviving with stable renal function during the first year.

	N	1-3 mo.	6 mo.	12 mo.
Group I	8	6	6	4
Group II	9	9	9	7

Serious infections occurred within 6 weeks of institution of therapy in 5 group I patients and one group II patient. Two group I but no group II patients had granulocyte counts below 500/mm^3. One group II patient developed insulin dependent diabetes while taking methylprednisolone.

Thus, although both forms of therapy appear to be effective acutely, treatment with megadose methylprednisolone may have a more favorable one year survival with fewer infections than treatment with plasma exchange.

VAGAL NEUROPATHY IN NON-DIABETIC HEMODIALYSIS PATIENTS. Ellen Burgess* (intr. by B.H.Scribner). Dept. of Medicine, University of Washington, Seattle, WA.

Heart rate variation is dependent upon an intact vagus nerve. Inherent beat-to-beat variability is expressed statistically by the mean square successive difference (MSSD). Sinus arrhythmia is expressed as the standard deviation (SD) of RR intervals. Nineteen normal volunteers and 19 non-diabetic hemodialysis patients (age 42.9±16.4 yr versus 44.9±15.2 yr) were assessed for vagal function by monitoring heart rate variation on resting electrocardiograms. Dialysis patients were studied pre- and postdialysis. In both normal and dialysis subjects RR interval did not vary with age. In normals, both MSSD ($p=0.02$) and SD ($p=0.009$) decreased with age, whereas in dialysis subjects there was no change with age ($p>0.3$). MSSD and SD were not statistically dependent upon RR interval. No significant difference existed between pre- and postdialysis studies. Comparison of dialysis patients to normal subjects revealed a significantly decreased ($p<0.001$) SD and MSSD in dialysis patients consistent with vagal denervation. The cause and extent of vagal neuropathy are unknown.

COLONIC CHANGES IN UREMIA. C. Caron, R. Detry, H. Haddad, B. Perey, G. Sanchez, S. Masse and G. Devroede, Univ. of Sherbrooke Hosp. Ctr., Dept. of Medicine, Sherbrooke.

The purpose of this study is to define uremic "colitis" as a clinical, proctoscopic and histological entity.

Four patients presenting diarrhea (group I) and 5 uremic controls (group II) were studied. Renal failure was of equal severity in both groups.

	BUN mg/dl	Cr mg/dl	C Cr ml/min
group I	104 ± 20	10 ± 2.5	5 ± 2
group II	95 ± 12	8.6± 1.4	6.5 ± 1.5

Clinically, diarrhea occured early or late in the course of the uremic syndrome. Uremic "colitis" was associated with severe complications of uremia (cardiac failure, pericarditis, ascites, cerebro vascular accidents and severe nephrosclerosis).

Endoscopically the first 15 centimeters above the anal margin were unremarkable. Above this point, sigmoid edema with polypoid mucosal protrusion was found.

The main histological features of uremic "colitis" were: focal edema of the lamina propria with vascular congestion, lymphoplasmocytic infiltration, increased mucous secretion, and fibrous thickening of epithelial basement membrane.

VISUAL LOSS IN RENAL DISEASE. M.M. Carim,* M.A. Pohl, and H. Zegarra.* Cleveland Clinic, Cleveland, Ohio.

A 25-year-old white female with Idiopathic Nephrotic Syndrome secondary to focal glomerulosclerosis and progressive renal insufficiency was admitted because of severe azotemia, fluid overload, and sudden decrease in visual acuity. Prior blood pressure (BP) determinations had been consistently≤150/100. On admission, BP was 160/108, BUN 130 mg%, serum creatinine 19.5 mg%. Bedside examination disclosed a near visual acuity of 20/20 in the right eye and count fingers in the left eye. Funduscopic examination of the right eye showed mild disc edema, diffuse retinal edema with scattered retinal infarcts and retinal hemorrhages. The left fundus showed more extensive, but similar findings, with sub-retinal fluid around the disc and retinal detachment in the macular area. These findings were consistent with the very poor vision in the left eye.

The patient received 4 dialysis treatments with concomitant fluid removal over 10 days, with a weight loss of 9 kg. The ultrafiltration resulted in prompt improvement in visual acuity, resolution of the retinopathy, and reattachment of the retina.

Patients with chronic renal failure, particularly those with massive edema and/or fluid overload, who complain of decreased vision, should have a prompt ophthalmological evaluation to rule out retinal detachment. Retinal detachment in such patients should be regarded as an immediate indication for fluid removal to expedite reattachment of the retina and maximize final visual acuity.

● EFFECTS OF 1,25-DIHYDROXYVITAMIN-D_3 ON RENAL FUNCTION OF CHILDREN WITH SEVERE CHRONIC RENAL DISSEASES. James C. M. Chan, Michael B. Kodroff* and Douglas M. Landwehr, Medical College of Virginia, Department of Pediatrics, Radiology and Medicine, Richmond, VA.

To test the question of possible deterioration in renal function secondary to treatment with 1,25-dihydroxyvitamin-D_3 and to establish the extent of the previously observed therapeutic benefits, studies were conducted in 11 children (aged 12 ± 4 yrs) with severe chronic renal disease (GFR 14 ± 11% of normal).

Reciprocal serum-creatinine concentrations for 32 months before treatment established the rates of progressive deterioration in renal function due to the primary renal diseases. Reciprocal serum-creatinine determinations at 2 to 6-month intervals prospectively for 32 months after initiation of 1,25-dihydroxyvitamin-D_3 p.o., at 15-35 ng/kg/day, indicated that treatment did not aggravate the rate of deterioration of GFR and in one patient, a slight improvement in renal functions was observed ($p<0.05$).

Mineral balance data after treatment with 1,25-dihydroxyvitamin-D_3 showed significant retention of calcium, phosphorus and zinc (579 ± 434 and 401 ± 74 mg/m^2/day and 86 ± 21 mcg/m^2/day, respectively) with restoration of serum calcium, alkaline phosphatase and PTH towards normal. After 6 months' therapy, healing of renal osteodystrophy was radiologically evident. Height-velocity of 8 children (73%) increased more than 2-fold over that expected. However, of the 3 older than 12 years, two failed to achieve accelerated growth velocity.

RENAL MANIFESTATIONS OF THE STAPHYLOCOCCAL TOXIC SHOCK SYNDROME. Russell W. Chesney, P. Joan Chesney,* and Jeffrey P. Davis.* Univ. of Wisconsin Med. School, Dept. of Pediatrics, Madison, WI.

Twelve women, aged 13 to 44 years, presented with fever (T ≥ 39.6°C), headache, confusion, erythroderma, sore throat, myalgias, diarrhea, hypotension (< 80/40) and thrombocytopenia. Symptoms began during menstruation in 11 and coagulase positive staphylococci were cultured from the vagina of 5 patients. Other features included a decline in hematocrit of 16±2 (SD)% with schistocytosis, oliguria for at least 24-36 hours in 11 patients. Mean serum creatinine (Cr) was 5.8 mg/dl and was > 2.6 mg/dl in 9 patients; mean BUN was 70 mg/dl. Sterile pyuria with sheets of cells was common. Although hematuria and proteinuria were present in 10 patients, RBC casts and a 24-hr urine protein excretion of > 1.0 gm was found in only 1 patient. Urinary electrolytes on admission in 3 patients revealed a U/P_{Cr} of < 20, a urine Na of > 50 mEq/L and a U/P_{osm} of < 1.1. Dialysis was required in one patient.

Hypoproteinemia and a serum albumin < 2.5 gm were found in 10 patients. Protein was not lost in urine and the low CVP and failure of 1-2 gm/kg albumin infusion to raise serum albumin concentration suggested a capillary "leak." All patients had edema. Early hypocalcemia and hypophosphatemia was seen in 10 patients and serum cholesterol was < 100 mg/dl. Following β-lactamase-resistant antibiotic therapy, recovery was rapid, and marked desquamation was seen in all. The differential includes leptospirosis, Kawasaki disease and hemolytic uremic syndrome. Renal features of this multisystem disorder are important and aid in rapid diagnosis and therapy.

POLYCYSTIC KIDNEY DISEASE (PKD) AND GENETIC MARKERS. D.N. Churchill, J.C. Bear,* D. Keeping,* W.H. Marshall,* J. Morgan,* R.H. Payne* and M.H. Gault. Faculty of Medicine, Memorial University, St. John's, Nfld. and Nfld. Blood Bank.

A search for genetic linkage between the loci for PKD and a number of polymorphic markers was performed in a 3 generation PKD kindred (I=10, II=47, III=68). Diagnosis was established from operative and autopsy reports, review of intravenous urograms or ultrasonography. Adequate information for diagnosis was available for 47 persons (I=9, II=29, III=9) of whom 32 had PKD. Blood was obtained for marker studies from 45/47. The following markers did not segregate and could not be used for linkage analysis: esterase D, 6-phosphogluconate dehydrogenase and Lutheran and Kell blood groups. The following markers did segregate but were uninformative for linkage study: ABO, Rhesus, Kidd and Lewis blood groups, gyloxylase-I and α-1-antitrypsin. Markers which did segregate informatively were HLA, haptoglobin and MNS$\bar{s}$ and Duffy blood groups. The HLA haptotypes in generation I were A3, B7; A29, B15, Cw3; A2, B18 and A9 and B12 and were designated a,b,c,d. For generation I all subjects with PKD and none without PKD had haplotypes, M$\bar{s}$, Fy^a and Hp-2. The frequencies of these haplotypes in the offspring of affected parents are shown in the table.

	a	b	c	d	M$\bar{s}$	Fy^a	Hp-2
PKD	4	4	3	6	3	2	2
No PKD	3	1	1	2	2	4	4

Those results suggest that linkage between the PKD locus and the loci for Duffy blood group, MNS$\bar{s}$, HLA and haptoglobin (Chromosomes 1,4,6 and 16) is unlikely.

IATROGENIC HYPERTENSION (HTN) IN POST-MENOPAUSAL OSTEOPOROSIS. Charles H. Chestnut, III,* David J. Baylink,* Clarice Cole,* and David A. McCarron (intr. by Donald Froom). Univ. Oregon Hlth. Sci. Ctr., Div. Neph., Portland Oregon; Univ. Washington, Div. Nuclear Med., Seattle, Washington; and Tacoma V.A., Div. Min. Metab., Tacoma, WA.

81 women (mean 65 yr.) participated in a 2-year study of the treatment of post-menopausal osteoporosis. All received 1.0-1.2 Gm of calcium (Ca) supplement q.d. and 1 of 3 drug regimens; placebo (N=38), 100 MRC units synthetic salmon calcitonin (CT) (N=24), or the anabolic steroid, stanozolol (SZ), 6 mg q.d. 3/4 weeks (N=19). Serum Ca, PTH (N-terminal assay), mean arterial pressure (MAP) (102±10 mmHg) and prevalence of HTN were similar in all 3 groups at initiation.

Both CT ($p<.001$) and SZ ($p<.001$) increased total body Ca as assessed by neutron activation, increased non-dialyzable urinary hydroxy-proline (CT, $p<.02$) (SZ, $p<.001$) and reduced % resorbing surface on iliac crest biopsy ($p<.001$). Serum Ca increased ($p<.01$) with both CT and SZ. However, PTH response differed significantly ($p<.001$) between CT and SZ. PTH was unchanged by SZ. With CT, PTH doubled ($p<.001$) over 2 years. Control's MAP was unchanged over 2 years. MAP response of the treated subjects differed significantly ($p<.01$). MAP fell to 93±31 mmHg with CT, while MAP increased to 112±11 mmHg ($p<.01$) with SZ.

In conclusion: 1) both CT and SZ were beneficial in post-menopausal osteoporosis, but differed importantly in their cardiovascular effects; 2) SZ significantly increased MAP while CT decreased MAP; 3) CT enhancement of PTH, an endogenous vasodilator, may account for the respective drug's divergent effect on blood pressure.

MYOGLOBINURIC ACUTE RENAL FAILURE ASSOCIATED WITH CHRONIC ETHANOL ABUSE. Rosa Clemente,* Deepak Nagar, Robert D. Lindeman, and Ronald L. Wathen. Univ. of Louisville, Dept. of Medicine, and Louisville VAMC, Louisville, Kentucky.

A patient with three well documented episodes of acute renal failure (ARF) associated with rhabdomyolysis and myoglobinuria was studied; phosphorylase and carnitine palmityl transferase deficiencies were excluded as etiologic factors. Only moderate chronic ethanolism insufficient to produce clinical evidence of cirrhosis was identifiable as a cause of recurrent myonecrosis. A review of 150 cases of ARF admitted to two hospitals over a three year period yielded 27 patients (18%) with ARF due to rhabdomyolysis and myoglobinuria. Twenty of these patients were confirmed chronic ethanol abusers. While other potential causes of myoglobinuric ARF could be identified in most of these patients, e.g. infections and sepsis (9), seizures, delerium tremens (3), trauma, drug abuse, shock, hypothermia (2) and such electrolyte disturbances as hypokalemia (4) and hypophosphatemia (4), several patients, including the index case, had no other identifiable cause. Many of these patients showed an accelerated increase in serum creatinine concentrations producing a low serum urea nitrogen/creatinine ratio, early hypocalcemia, late hypercalcemia, and accentuated hyperkalemia, hyperphosphatemia and hyperuricemia. The outcome appeared to be influenced by the presence of other etiologic factors, e.g. infection, sepsis and shock, with 13 of 20 alcoholics recovering from their ARF. This study documents the importance of ethanol abuse as a cause of myoglobinuric ARF.

PNEUMOCOCCAL VACCINATION OF CHRONIC RENAL DISEASE PATIENTS AND RENAL ALLOGRAFT RECIPIENTS. F. Cosio*, G. Giebink*, T. Davin, G. Schiffman*. Dept. Med. & Ped., Univ. of Minn., Minneapolis, MN and Dept. Microbiol., Downstate Med. Ctr., Brooklyn, NY.

Polyvalent pneumococcal vaccine (PV) was administered to 7 patients with chronic renal failure (CRF); 14 patients on chronic hemodialysis (CHD); 14 splenectomized (Sx) and 11 nonsplenectomized renal allograft (RA) recipients; and 14 normal adults. Serum pneumococcal antibodies to 12 capsular antigens were measured by radioimmunoassay. Geometric mean (GM) antibody levels before PV were lower in RASx and RA patients than in normals, and they were directly related to the interval between transplantation and antibody determination. Ninety-three percent of normals had at least a two-fold rise in antibody levels after PV and an antibody level after PV greater than 200 ngN/ml. Forty-three percent, 79%, 78% and 55% of CRF, CHD, RASx, and RA patients respectively achieved similar responses. RASx and RA patients had adequate fold rise in antibody levels after PV but had lower GM post PV antibody levels than normals.

	GM antibody (ng antibody N/ml) (95% CI)	
Disease	Pre-Vaccination	Post-Vaccination
Normals	313 (253-287)	1113 (937-1323)
CRF	328 (210-514)	762 (451-1286)
CHD	263 (181-382)	754 (510-1116)
RASx	158 (106-236)	557 (412- 753)
RA	67 (21-214)	268 (109- 660)

These results suggest that PV may be efficacious in CHD patients and RA patients vaccinated more than 6 months after transplantation. Uremic patients are poor responders to PV, and PV may not provide effective prophylaxis in these patients.

POSITIVE IMMUNE STAINING OF PERICARDIUM IN UREMIC PERICARDITIS. Michael Culpepper, Patricia Adams, Richard McElvin*, Dept. of Med. and Dept. of Surg., Univ. of Ala., Birmingham, AL.

Uremic pericarditis is a common complication of chronic renal failure (CRF). This study seeks to establish whether immune events identified by immunoglobulin deposition in uremic pericardium might play a role in the inflammatory process. Pericardial tissue obtained at surgery from patients undergoing total pericardiectomy for cardiac tamponade or increasing effusion unresponsive to daily dialysis was stained with fluorescent-labeled antibody by standard techniques. Eight patients were studied; 4 had never undergone dialysis and 4 had been on maintenance hemodialysis 5x/2 weeks for an average of 24.5 mos (range 5-60 mos). The etiology of renal failure varied. Gross pathology showed fibrinous pericarditis in all cases but one. Immunofluorescence showed faint non-specific staining for albumin equal to that seen in renal biopsies. Fibrinogen was present in all 8 pericardia. Three specimens were positive for C-3 but not C-4 suggesting alternate pathway activation of complement. IgG was the most prominent immunoglobulin in 6 specimens; IgA and IgM in one each. Three cases had significant IgA in addition to IgG; IgM was notable in only 2 cases. The case without fibrinous exudate was negative for C-3 and C-4. We conclude that the immune system may play a role in the genesis of uremic pericarditis. The variable immunologic patterns suggest that pericardial inflammation may be the common result of multiple processes in a uniquely susceptible host. The etiology of the CRF does not seem related to the pericardial staining. Finally nonfibrinous pericarditis may occur in CRF and not involve immune mechanisms.

GROWTH FAILURE AND RENAL TUBULAR ACIDOSIS IN CYANOTIC CONGENITAL HEART DISEASE. John F.S. Crocker, Maurice A. Nanton* and C. Siqueira*. Dalhousie Univ. and the Izaak Walton Killam Hospital for Children, Dept. of Pediatrics, Halifax, Nova Scotia.

Growth failure in children with cyanotic congenital heart disease (CCHD) remains a problem in the management of these patients. We observed that some of our patients with CCHD had renal tubular acidosis (RTA). Since patients with RTA as an isolated lesion fail to grow normally we felt that we should investigate patients with CCHD to look for a possible association between the presence of RTA in CCHD and failure to thrive. In this preliminary report, 9 stable patients with CCHD were assessed for RTA. NH_4Cl loads and bicarbonate reabsorption studies were carried out with baseline acid base studies of blood and urine. Seven patients had proximal RTA and no patient had distal tubular acidosis. Two patients who had RTA and were awaiting surgery were placed on oral bicarbonate. This did not, however, seem to affect their growth. One case has since gone for corrective surgery and now has a normal acid base status. Bjarke et al. have noted in adults with Tetralogy of Fallot that 3/11 patients had proximal RTA. Our numbers are too small to assess the effect of correcting RTA on growth. The study does show a high incidence of RTA in CCHD.

SIMULATION OF THE RENAL EFFECTS OF WEIGHTLESSNESS USING ANTI-SHOCK TROUSERS. G.M.Danovitch, A.Licht, R.Bowman*and N.S. Bricker. Renal Division, UCLA School of Medicine, Los Angeles, California

Negation of the normal gravitational forces that are present in the upright position produces a cephalad redistribution of ECF and induces natriuresis. This phenomenon has significance for understanding the volume control mechanisms in normal and pathological states and is also responsible in part, for the weight loss and natriuresis that occur during prolonged space flight. To date, this natriuresis has been investigated using two techniques; bedrest and water immersion. The present studies describe a new method of simulating the volume effects of weightlessness. Jobst anti-shock trousers (AST), which are used clinically in the treatment of shock were applied to eight normal supine males. Pressures were maintained at 45 mmHg in the legs and 20 mmHg in the abdomen. Urine sodium excretion ($U_{Na}V$) rose from 148±29 μEq/min in the control (pre-inflation) hour to 248±33 μEq/min after one hour and 282±41 μEq/min after two hours of inflation. Urine volume doubled, in part due to an increase in free water clearance. In separate studies subjects remained supine but without AST inflation. The natriuresis of bedrest ensued but was significantly less pronounced than with AST. The natriuresis and diuresis produced by AST are presumably initiated by a redistribution of ECF into the thorax in a manner analagous to that observed during water immersion. This translocation helps explain the value of AST in the treatment of clinical shock and provides a further method for evaluating both the afferent and efferent components of the volume control system.

THE PITUITARY-THYROID GLAND AXIS IS NORMAL IN CHRONIC RENAL FAILURE (CRF). F.B. Davis,* D.A. Spector, B.R. Hirsch,* J.J. Walshe and P.J. Davis. SUNY at Buffalo School of Medicine, Buffalo, NY, Baltimore City Hospitals and Johns Hopkins University School of Medicine, Baltimore, MD.

Testing of pituitary-thyroid gland function with thyrotropin-releasing hormone (TRH) in CRF patients has been reported to result in reduced thyrotropin (TSH) secretion despite low serum triiodothyronine (T_3) levels, perhaps due to a hypothalamic defect. "Reduced" TSH secretion in CRF, however, has been defined in relation to control subjects who were not age- and sex-matched with CRF patients. We have studied TRH-responsiveness (500 µg TRH i.v. bolus) and release of T_3 in response to endogenous TSH in 14 dialysis outpatients and have compared performance with 14 age- and sex-matched outpatient controls with normal renal function (serum creatinine, <1.2 mg/dL):

Serum TSH content (µU/mL)	Basal ($\bar{x}$±SE)	30 min	Post-TRH 60 min	90 min
CRF	5.5±0.7	11.0±3.2	11.8±2.9	11.4±3.4
Controls	4.5±0.7	11.6±1.5	10.4±1.6	8.0±1.2
P	NS	NS	NS	NS

CRF and control patients showed identical increases (27.0 and 26.8 ng/dL, respectively) in serum T_3 content after TRH administration, although absolute serum T_3 levels were consistently lower in CRF patients.

Conclusions: Compared to age- and sex-matched controls with normal renal function, CRF patients have normal TRH responsiveness and normal thyroid gland response to endogenous TSH. In terms of the pituitary-thyroid axis, CRF patients can be characterized as having normal hypothalamic function.

RENAL TUBULAR ACIDIFYING DEFECT IN TUBULOINTERSTITIAL DISEASE OF LUPUS NEPHRITIS. John Fennell, M.M. Schwartz, A.K. Bidani, and E.J. Lewis. Rush Medical College, Chicago, Illinois.

We have studied the tubulointerstitial lesions in 52 patients with lupus nephritis (LN). The incidence and severity of these lesions were correlated with the ability of the tubules to maintain normal acid-base balance. The pathological findings were assessed independently and graded on a semi-quantitative scale. The incidence of low serum bicarbonate (<22 mEq/L) in the LN patients (15/52) was significantly higher than in 47 patients with non-lupus glomerulonephritis (3/47; $P<0.01$). The serum creatinine in the two groups was not different (1.49 ± 0.17 and 1.53 ± 0.17; $P>0.1$). Patients with LN were divided in 2 groups: (I) those with bicarbonate below 22 mEq/L (mean 19.05 ± 0.68); (II) those with bicarbonate greater than 22 mEq/L (mean 26.17 ± 0.51). Although the serum creatinine in group I (2.49 ± 0.41) was significantly higher than in II (1.08 ± 0.13; $P<0.01$), the anion gap was not significantly different between the two groups, being normal (<14) in 14/15 group I patients. The difference in histopathological findings between the groups consisted of more extensive interstitial inflammatory infiltrates in group I (mean score 1.73 ± 0.25) compared to group II (mean score 0.73 ± 0.12). Similarly, interstitial fibrosis was more pronounced in I (1.53 ± 0.26) vs II (0.84 ± 0.15). Immune aggregates were present in the interstitium and around tubular and vascular structures in approximately one half of each group. We conclude that a renal tubular acidifying defect is frequently seen in LN. It is associated with mild renal impairment and with more severe tubulointerstitial disease.

PREVALENCE OF DIABETIC NEPHROPATHY COINCIDENT WITH KNOWN RETINOPATHY. J.N. Feldman,* M.M. Beyer, S. Hirsh,* G. Charles,* F.A. L'Esperance, Jr.,* W.A. James,* E.A. Friedman. Downstate Medical Center and College of Physicians & Surgeons, N.Y., N.Y.

We evaluated the correlation between diabetic retinopathy (DR) and "silent" nephropathy. A total of 46 nondiabetic (ND) (mean age 58.2 yrs., range 17-86) and 111 diabetic (DM)(mean age 52.19 yrs, range 19-81) patients were studied. The population included 56/111 (50%) DM with onset at age 30 or less, and 66/111 (59%) who had been diabetic for 20 or more years. Of the 111 subjects, 106 (95%) had background and/or proliferative retinopathy. ND patients had eye diseases other than DR. Testing included urinalysis venous BUN and serum creatinine (Cr) concentrations.

Of 21 (19%) of DM who recalled previous testing for kidney disease only 3 (2%) had been told of clinically significant renal dysfunction. 13% (14/108) of DM as opposed to 2.6% (1/38) of ND were found to have Cr levels >2mg/dl (<0.05). None of the ND had urinary protein excretion >100mg/dl but 21% of the DM had at least this degree of proteinuria ($p<.01$). An increased BUN (>30mg/dl) was noted in 24% (26/108 of DM, and 5.2% (2/38) of ND ($p<0.02$). Diastolic blood pressure >95mmHg was present in 26% (31/102) of DM and 5% (2/40) of ND ($p<0.01$). Systolic hypertension (>160mmHg) was also more prevalent in DM 29% (30/102) than in ND 23% (9/40) (N.S.).

We concluded that undetected, significant nephropathy is present in a substantial proportion of diabetics with clinically apparent retinopathy. The previously noted universal association of diabetic retinopathy with nephropathy does not obtain in patients evaluated first for retinopathy.

COMPARISON OF NEPHROTOXICITY ASSOCIATED WITH NETILMICIN (N) AND AMIKACIN (A) IN CANINES. N.E. Gary, M. Snyder*, and A. Bretschneider*, CMDNJ-Rutgers Medical School, Piscataway and W. Burns* CMDNJ-Rutgers Medical School and V.A. Medical Center, Lyons, New Jersey.

Nephrotoxicity of N and A was compared in canines given various doses over 14 days. Four groups of 7 dogs received 7.5, 15, 30 mpk of A or 3, 6, 12 mpk of N or saline intramuscularly every 12 hours. Creatinine clearance, BUN, urinary protein excretion were normal at the outset and end of study. Of 16 dogs given the 2 highest doses of A and N, granular casts appeared during the study in 14 and increased in number in 2 animals. Accumulation of the drug in serum was noted in one dog at each N dose level and one given A 60 mpk/day, after 14 days. Despite some minor variation within dosage groups there was no substantial difference in the degree or extent of renal injury caused by A or N at any dose level by light microscopy. Electron microscopy showed increased size and number of lysosomes in proximal tubular cells with some foci of necrosis in dogs at the lowest doses of A and N despite absences of lesions by light microscopy in the A group. The extent of renal injury at the highest and middle doses was very similar but more than observed at the lowest doses.

It is concluded that 1) in canines A and N caused minimal and comparable histological renal change, 2) appearance of or increased numbers of granular casts were the only observed clinical manifestation of toxicity, 3) injury did not appear to be related to drug accumulation in serum.

PROGRESSION OF NIL DISEASE TO FOCAL GLOMERULAR SCLEROSIS IN THE PRESENCE OF HODGKIN'S LYMPHOMA. Wallace C. Gauntner, Irene Stachura, and Edmund Bourke. Renal-Electrolyte Division and Department of Pathology, Allegheny General Hospital, Pgh., PA

The relationship between Nil Disease (N.D.) and Focal Glomerular Sclerosis (F.G.S.) has been an on-going issue of controversy. Whether they represent 2 discrete pathologic entities or are manifestations of a single process is unresolved.

This patient presented with the Nephrotic Syndrome (N.S.). Renal biopsy containing corticomedullary glomeruli demonstrated N.D. Despite steroid therapy the N.S. persisted (25 gm/day) and renal insufficiency (P_{Cr} 3.5 mg%) developed within 5 months. Repeat biopsy revealed F.G.S.

	LIGHT	IF	EM
Bx #1	Normal	Neg.	Diffuse foot process fusion
Bx #2	Focal and segmental Glomerular Sclerosis Focal Interstitial Nephritis	Focal and segmental IgM, C3	Diffuse foot process fusion Segmental increase in mesangial matrix

One month later, lymph node biopsy revealed Hodgkin's lymphoma, nodular sclerosing type. Following combined chemotherapy (MOPP), P_{Cr} fell from 3.5 mg% to 1.0 mg% and 24 hour U_{Pr} from 25 gm to 0.9 gm. In our patient, F.G.S. was preceded by N.D. Its occurence in the presence of lymphoma and improvement after chemotherapy may reflect an immune mediated disorder. The histology of N.S. in Hodgkin's Disease is usually N.D. The progression to F.G.S. in the present report supports the concept that both conditions are manifestations of a single process.

REVERSAL OF CHRONIC RENAL FAILURE (CRF) IN PROGRESSIVE SYSTEMIC SCLEROSIS (PSS) WITH CAPTOPRIL (C). Stephen Graham*, David Goodman*, Ed Dubois*, and Marshal Fichman. Cedars-Sinai Medical Center, Div. of Nephrology, Los Angeles, California.

In the past patients with PSS and CRF have been successfully maintained by a combination of antihypertensive therapy or nephrectomy and hemodialysis (HD). We have observed a patient who showed dramatic improvement in renal function to the point of terminating HD with only C therapy for hypertension (HTN). The patient is a 30 y.o. white female with a previous history of + ANA's, arthralgias, and sclerodermatous skin changes but normal blood pressure and normal renal function presented with a BP 190/130, pulmonary edema, and papilladema. HTN was initially controlled with nitroprusside therapy but renal function deteriorated and a renal biopsy revealed myxoid intimal sclerosis of the small arteries most consistent with PSS. Serum renin conc. was markedly elevated at 163 ng/ml (nl 11-23 ng/ml). HD was initiated when the serum Cr reached 8.8 mg/dl. HTN was poorly controlled on maximal doses of alpha-methyldopa and hydralazine, and C therapy was started. BP promptly decreased to less than 130/80 on a regimen of 25 mg/d. Urine output increased and over the ensuing ten months a progressive decline in pre-dialysis serum Cr was noted; HD was discontinued. The patient has maintained a serum Cr of less than 3.4 mg/dl and BP less than 130/80 on C alone for over six weeks. Anti-hypertensive therapy with Captopril in PSS may allow reversal of CRF in some patients.

PLASMAPHERESIS FOR LUPUS NEPHRITIS WITHOUT DEMONSTRATION OF CIRCULATING IMMUNE COMPLEXES. R.M. Gipstein, D.A. Adams, M.T. Grabie, J.T. Shere and J.B. Peter*,Dept. of Medicine (Nephrology & Rheumatology), Santa Monica Hospital, Santa Monica, CA

The prevailing explanation for the success of plasmapheresis (Pp) in lupus nephritis involves the removal of circulating immune complexes (CIC's) during the plasma exchange (PE). We recently used PE successfully in 2 Mexican-American females, age 25 and 15, with lupus nephritis but no detectable CIC's. Both patients had the nephrotic syndrome and progressive azotemia (secondary to biopsy proven diffuse proliferative glomerulonephritis) despite immunosuppressive therapy with azathioprine and corticosteroids, administered orally and intravenously. Serum creatinine rose to levels between 6-7mg/dl and BUN to 120-150mg/dl before each patient underwent hemodialysis. Both patients had high titers of antinuclear antibody and native DNA binding. The older patient had lupus vasculitis with accelerated hypertension and seizures. Both had crescent formation, the younger patient exhibiting crescents in all 12 glomeruli viewed. Immunofluorescent studies on both renal biopsies revealed IgG, IgA and IgM with C_3 and C_{1q} deposits. A skin biopsy in the older patient showed similar deposition. Despite this evident renal deposition of complement fixing immune complexes, soluble CIC's could not be detected by precipitation with 4% polyethylene glycol, by solid and liquid phase C_{1q} assays, and in the older patient, by Raji cell assay. Progressive azotemia was abated and reversed with 4 L PE on an intensive schedule, allowing discontinuation of hemodialysis. Pp should not be withheld even in the absence of CIC's or when crescents involve 100% of the glomeruli seen on renal biopsy.

CLINICO-PATHOLOGIC CORRELATIONS IN SEGMENTAL NECROTIZING LUPUS NEPHRITIS. Edith Grishman and Jacob Churg. Mount Sinai School of Medicine, Dept. of Path., New York, N.Y.

One of the manifestations of lupus nephritis is segmental areas of necrosis in the glomeruli. Such lesions may occur as an isolated or almost pure manifestation, or as part of a more diffuse glomerulonephritis. Their significance is uncertain. Some investigators regard them as a mild process, while others classify them as severe disease and an index of poor prognosis.

In an attempt to resolve this question, we have followed 15 patients with segmental lesions and only minor other changes in the glomeruli, for an average of 6 years (2 to 20 years). All patients were treated with steroids. During the period of follow-up, 2 patients went into renal failure, 3 others developed mild stable renal insufficiency (creatinine 2.2 - 2.5) and the remaining 10 patients retained good renal function, including 4 who were followed for 8, 9½, 14 and 20 years respectively. There was no clear-cut relationship between the extent of glomerular involvement and the outcome of disease: Patients who developed mild renal insufficiency showed initially a higher average percentage glomerular involvement, but the 2 patients who went into renal failure had less initial involvement than those who maintained normal renal function. The lesions tended to heal by fibrosis without significantly affecting the remainder of the glomerulus. It is concluded that when treated, segmental necrotizing lesions have good outcome. The pathogenesis of these lesions may be different from other changes in lupus nephritis.

● AMILORIDE IN THE TREATMENT OF BARTTER'S SYNDROME AND LIDDLE'S SYNDROME. H.-G. Gullner and F.C. Bartter. Dept. of Med., UTHSC and VA Hospital, San Antonio, TX.

Bartter's syndrome is characterized by hypokalemic alkalosis, hyperreninemia, aldosteronism and normal blood pressure. The clinical features of Liddle's syndrome consist of hypokalemia, suppressed plasma renin activity and aldosterone secretion rate and hypertension. The proximal cause of Bartter's syndrome has been shown to be a defect in chloride reabsorption in the distal tubule; an increase in distal sodium transport has been postulated to be the primary abnormality in Liddle's syndrome. We studied the effect of amiloride, a diuretic which inhibits sodium transport and potassium secretion in distal nephron segments in vitro, on potassium metabolism in 2 women with Bartter's syndrome and 2 women with Liddle's syndrome. The patients were admitted to a metabolic ward and were fed constant metabolic diets containing 109 mEq/day sodium and 40-60 mEq/day potassium. After an 8-day control period, amiloride, 5 mg q.i.d., was given for 4-8 days. In Bartter's syndrome, amiloride increased mean serum potassium from 2.2 $\pm$ 0.1 mEq/L to 4.0 $\pm$ 0.3 mEq/L ($p<0.05$) and decreased mean urinary potassium excretion from 66 $\pm$ 4 mEq/day to 35 $\pm$ 3 mEq/day. In Liddle's syndrome, amiloride increased mean serum potassium from 3.3 $\pm$ 0.05 mEq/L to 4.9 $\pm$ 0.2 mEq/L ($p<0.05$) and decreased mean urinary potassium from 51 $\pm$ 1 mEq/day to 27 $\pm$ 2 mEq/day. Amiloride decreased blood pressure in one patient from 160/102 mm Hg to 120/90 mm Hg. Serum sodium was not significantly affected in any patient and urinary sodium excretion increased only slightly. The data indicate that amiloride may correct hypokalemia in these disorders by inhibition of potassium secretion in the distal tubule.

LOW INCIDENCE OF MALIGNANCY ASSOCIATED WITH NEPHROTIC SYNDROME IN THE ELDERLY: W. Heneghan,* T.K.S. Rao, A.D. Nicastri, E.A. Friedman. Downstate Medical Center, Brooklyn, New York.

De novo onset of a nephrotic syndrome in elderly patients has been thought to indicate occult malignancy in a substantial subset.

In order to test the thesis, we ascertained the difference in the etiology of the Nephrotic Syndrome (NS) and the prevalence of associated malignancy in 21 non-diabetic nephrotic patients who were over 60 years of age compared with 68 other nephrotic patients between the ages 20 and 59. In all, a renal tissue diagnosis to explain NS was available, and the results are tabulated below.

	Age > 60 (n = 21)	Age < 60 (n = 68)
Amyloidosis	14%	4%
Membranous GN	38%	12%
Lipoid Nephrosis	14%	13%
Focal Sclerosis	19%	19%
Lupus Nephritis	5%	23%
Membranoprolif. GN	0	15%
Others	10%	13%

Malignancy (carcinoma of large bowel) was found in only one patient with lipoid nephrosis who was 68 years old. From these data, we conclude. (1) While amyloidosis and membranous GN are more common causes of NS in those over age 60, lupus nephritis and membranoproliferative GN is more prevalant in younger patients. (2) The incidence of lipoid nephrosis and focal sclerosis was similar in both the age groups. (3) The association of malignancy with NS, even in those over the age 60 is rare.

HYPERCALCEMIA DURING THE DIURETIC PHASE OF ACUTE RENAL FAILURE. R. Hellman, T. Johnson, and R. E. Wahman*. Duluth Clinic, Ltd., Duluth, Minnesota.

Hypercalcemia (H) occurs in 20-24% of cases in the diuretic phase (D) of acute renal failure (ARF) due to rhabdomyolysis (R). Three basic mechanisms have been offered to explain this H: 1) transient secondary hyperparathyroidism, 2) immobilization and 3) remobilization of previously deposited calcium in damaged muscles.

We investigated 3 cases of oliguric ARF due to R. All required dialysis and had complete return of renal function. All were initially hypocalcemic and 2/3 developed H (14.0-15.2 mg/dl) occurring 4-5 days after the initiation of the D of ARF with a duration of 6-6.5 days. Measurement of serum immunoreactive parathyroid hormone (iPTH), tubular reabsorption of phosphorus (TRP), and 24 hr. urine calcium (24 hr U Ca^{++}) either at the peak of H or 5 days after the initiation of the D of ARF was performed in all patients. TRP was decreased in all initially (11-70%). iPTH was absolutely increased in 1 patient and relatively increased in a second patient, both of whom were hypercalcemic. 24 hr U Ca^{++} was increased in both patients with H. Xeroradiography and Technecium 99 pyrophosphate scanning performed in 2 patients were negative in the normocalcemic patient and positive in a patient who became hypercalcemic. All patients had normal calcium and phosphorus in the recovery phase of ARF, and in the one patient tested the elevated iPTH and decreased TRP returned to normal. H responded to saline infusion and was not associated with increased morbidity.

These data suggest that the H seen in the D of ARF is due to remobilization of previously deposited calcium in damaged muscle in association with transient secondary hyperparathyroidism.

● BONE ALUMINUM IN OSTEOMALACIC RENAL OSTEODYSTROPHY CORRELATION WITH EXCESS OSTEOID. A.B. Hodsman*, D.J. Sherrard, A.S. Brickman, A.C. ATfrey, W.G. Goodman, N. Maloney*, D.B.N. Lee and J.W. Coburn. V.A. Wadsworth, Sepulveda, Seattle & Denver Med. Ctrs., UCLA Sch. Med., Univ. Wash., & Univ. Colo. Los Angeles, CA.

The cause of the sporadic syndrome, dialysis osteomalacia (OM) with fractures but no secondary hyperparathyroidism, is unknown. Because outbreaks of OM have been associated with excess aluminum (Al) in dialysate, we measured bone Al in 49 of >250 biopsies obtained from hemodialysis (HD) patients with bone disease; 18 had osteitis fibrosa (OF) and 13 had mixed lesions (M) OM+OF; the 18 OM represented <2% of HD patients referred from 13 centers. Biopsies were classified by quantitative histomorphometry: osteoid area was 30.5±4.2% of total bone area in OM, 8.8±1.1 in OF, and 19.2±4.5 in M, (Normal, 3.68±1.41 SD). In OM, bone Al was 162±18 SE mg/kg dry weight; it was 63±9 in OF and 57±10 in M, both below OM ($p<.001$). Bone Al correlated with osteoid area in OM ($r=0.92$) but not in OF or M. No correlation existed between bone Al and fibrosis or resorbing surfaces. The duration of HD was longer in OM compared to the total OF+M: 7.1±1.3 vs 4.2±.39 yrs. ($p<.05$); but bone Al did not correlate with the duration of HD in OM. These data show an association between bone Al and OM in HD patients independent of parathyroid bone status. The reason for Al accumulation is unclear, but Al may accumulate preferentially in bone of azotemic patients and act to inhibit mineralization. The route of Al assimilation by patients with sporadic OM remains unclear; its low prevalence suggests a host factor may be operative.

PREDICTION OF AN ABNORMAL RENAL ANGIOGRAM IN PATIENTS WITH HYPERTENSION.
Horvath J.S.,* Tiller D.J.,* Duggin G.G.,* Waugh R.,* and Roy L.P.

A review of the records of 490 patients with hypertension submitted to renal angiography (RA) on the basis of one or more of the following:- age <40 years, hypertension difficult to control, renal impairment; was carried out looking for features which might predict abnormal renal angiography (ARA).

Three hundred and eighteen RA were entirely normal, including all 82 males whose sole indication for study was age <40 years.

There was a high yield of ARA (182 of 490), of whom 76 had insignificant stenosis (< 75%) and 45 had parenchymal renal disease. The patients with ARA, compared with the patients with normal RA were significantly ($p<0.05$) older, (46.3 ± 0.9 vs 37.3 ± 7 years), had longer-standing hypertension (7.4 ± 0.6 vs 4.8 ± 0.4 years), had more severe hypertension (mean arterial pressure 118 ± 1 vs 110 ± 1.2 mmHg), had significantly worse renal function (serum creatinine 245 ± 21 vs 116 ± 6 µMol/l), and more commonly abused analgesics (47% vs 14%).

These results suggest that the younger male with well controlled hypertension does not require RA, and that ARA is more likely in patients who are older, have poorly controlled hypertension, have impaired renal function or abuse analgesics. However no single parameter was diagnostic of ARA in the individual patient.

USE OF A CLONAL ASSAY SYSTEM TO PREDICT THERAPEUTIC RESPONSE TO STEROIDS IN THE ANEMIA OF CHRONIC RENAL FAILURE (CRF).
Maria Kalmanti,* Joseph Martino, Maureen Callahan,* Nicholas Dainiak,* St. Eliz. Hosp., Dept. of Res. & Med., Boston, Mass.

Although steroids may improve anemia in CRF, they are frequently ineffective. A method to select patients (pts) for this therapy would not only reduce steroid hepatotoxicity but also reduce the morbidity and high cost of chronic transfusions. We utilized a hormone-depleted, clonal assay system for the growth of erythroid stem cells to assess steroid response in bone marrow cultures from 6 volunteers and 6 dialysis pts with hypoproliferative anemia (mean Hb of 7.6 gm/dl) and stable CRF. Nutritional deficiencies and active hemolysis were absent. Three pts had a favorable hematologic response to steroids (Hb rise of 2 gm/dl to >10 gm/dl and relief of anemic symptoms) and 3 pts were clinically unresponsive. Erythroid colony formation (ECF) by normal marrow (55 ± 14 colonies/6x10^4 cells) was enhanced by 85 - 120% above ECF in control cultures by steroids of 4 classes. ECF by marrow from the 3 clinically responsive pts (51 ± 10 colonies/6x10^4 cells) was similarly augmented (35-100% increase). However, ECF by marrow from the 3 clinically unresponsive pts was either markedly reduced (8 ± 2 colonies/6x 10^4 cells) or insignificantly altered (0-5% increase) by steroids of the same class used clinically. We suggest that this in-vitro clonal assay system may be useful in predicting a therapeutic response to steroids in pts with the anemia of CRF. It appears that pts having erythroid stem cells which proliferate normally and which retain normal sensitivity to steroids in-vitro, are likely to have a favorable clinical response to these agents.

THE EFFECTS OF INDOMETHACIN ON RENAL CONCENTRATING AND DILUTING CAPACITY IN SICKLE CELL NEPHROPATHY.
P.E.de Jong*,L.T.W.de Jong-van den Berg*,H.Schouten*,A.J.M.Donker*,L.W.Statius van Eps.Dept.of Med. State University,Groningen,The Netherlands.

Recently we demonstrated that prostaglandins have an important role in maintaining a normal GFR and ERBF in sickle cell anaemia (SCA).Indomethacin (I) was also found to give an increase in fractional urea reabsorption with a rise in serum urea in SCA (Clinical Science,in press).We therefore studied the influence of I on renal electrolyte transport during maximum diuresis and antidiuresis. In water-deprived control subjects I induced a rise in maximum urinary osmolality (Max Uosm of 836 to 1027 mOsm/kg H_2O,while Max Uosm did not change after I administration in SCA (419 before and 409 mOsm/kg H_2O after I),notwithstanding a decrease in diuresis of 1.5 to 0.8 ml/min. I administration in water-loaded SCA-patients led to an increase in Uosm from 42-125 mOsm/kg H_2O,while I in the diluted control subjects did not influence Uosm (59 and 63 mOsm/kg H_2O before and after I,resp.). I induced a sodium, potassium and chloride retention in both the water-loaded and -deprived control subjects and SCA patients. Fractional urea reabsorption increased in the water depleted control subjects and SCA patients,while it did not change in the water-loaded situation. In all situations there was a phosphaturia after I. We conclude that I promotes sodium reabsorption in the ascending limb of Henle's loop. The defect in renal concentrating capacity in SCA cannot be influenced by I,which is further proof of a defect in the trapping of solute in the medulla in SCA. Finally,prostaglandins protect the SCA-patient against a dilutional hyponatraemia, which suggests a state of increased vasopressin concentration for the existing serum osmolality in SCA.

INTRAGLOMERULAR THROMBOSIS: A FORERUNNER OF GLOMERULAR SCLEROSIS.
K. S. Kant, H. I. Glueck*, M. S. Weiss,* and V. E. Pollak. University of Cincinnati Medical Center, Cincinnati, Ohio.

Factors leading to glomerular sclerosis (GS) are not understood. In systemic lupus erythematosus (SLE) renal lesions may be mediated by immune complex deposition, complement activation, and intravascular coagulation. To assess the role of thrombosis, a semiquantitative analysis of 105 renal biopsies from 71 patients, including 9 with circulating anticoagulants (CAC), with SLE was made. Thrombi were diagnosed by light microscopy in Lendrum stained sections, and were concordant with fibrin positive material by immunofluorescence ($\chi^2=23$; $p<0.001$). In SLE with CAC, glomerular thrombi were present with no necrosis ($p<0.001$) or subendothelial deposits ($p<0.005$); serum C3 and anti-dsDNA antibody levels were normal. Patients with glomerular thrombi but no CAC had low C3 and elevated anti-dsDNA antibody levels. Platelet counts <175,000/mm^3 were found with glomerular thrombi ($p<0.001$) and subendothelial deposits ($p<0.05$), but not with glomerular necrosis. In patients with thrombi, Factor VIII levels were increased ($p<0.05$). In 24 patients studied sequentially, progression of GS in a second biopsy was associated with thrombosis ($\chi^2=8.4$; $p<0.005$) and with subendothelial deposits ($\chi^2=3.6$; $p<0.06$) in the first, but not with crescents, necrosis, endothelial or mesangial cellularity, or subepithelial deposits ($\chi^2<1$ in all; $p>0.3$). Thus, in SLE: 1) glomerular thrombosis may be predicted by a low platelet count and high Factor VIII level; 2) coagulation may occur with immune or non-immune mechanisms; 3) thrombosis, but not necrosis leads to GS.

THYROID HORMONE INDICES IN ACUTE RENAL FAILURE (ARF). E.M. Kaptein,* D. Levitan, E.I. Feinstein, J.T. Nicoloff,* and S.G. Massry. Div. Neph. and Endocrinol., USC Sch. Med., Los Angeles, Calif.

Disturbances in thyroid hormone indices occur in chronic uremia, but the effect of acute renal failure is not known. Thirteen patients were studied during the course of ARF and after recovery of renal function. ARF was due to non-traumatic rhabdomyolysis in 11 of 13. During the oliguric phase serum total T_4 levels were reduced to 5.4±0.6 μg/dl (±SEM, normal: 8.0±0.1, $p<0.02$). TBG assessment and free T_4 values remained normal. Total T_4 levels correlated inversely with serum creatinine during oliguria ($r=0.9$, $p<0.05$). A rapid rise in total T_4 occurred with the fall in serum creatinine beginning with the diuretic phase. Serum T3 was reduced during both the oliguric (53±7 ng/dl, $p<0.01$) and diuretic (72±10 ng/dl, $p<0.01$) phases and increased to 118±14 ng/dl when serum creatinine returned to normal. Total reverse T3 (rT3) levels were within the normal range in 11 of 13 patients during the oliguric and diuretic phases. Free rT3 levels were elevated in most patients during this time. Basal TSH levels were normal but the response to TRH was blunted during the oliguric phase compared to recovery. The data show that in ARF: 1) changes in thyroid hormone indices are frequent and occur shortly after onset of illness, 2) defective binding of T_4 and rT3 to carrier proteins is present, 3) the inverse relationship between T3 and rT3 seen with other nonthyroidal illnesses is absent. rT3 is not elevated in chronic renal failure as well, despite low T3, suggesting a role for the kidney in rT3 production.

A CLINICOPATHOLOGICAL STUDY OF LITHIUM NEPHROTOXICITY. Priscilla S. Kincaid-Smith, Rowan G. Walker, Brian M. Davies. Dept. of Nephrology & Univ. Dept. of Psychiatry., Royal Melbourne Hospital, Victoria, Australia.

Lithium salts, well recognized as acute nephrotoxins, have been implicated as a cause of chronic focal interstitial nephropathy. We previously reported an acute specific distal tubular lesion in patients of lithium therapy (Burrows et al, Lancet 1, 1310, 1978). In a clinicopathological study of lithium nephrotoxicity, renal function and renal histology has been compared between 25 patients on maintenance lithium therapy (Li) and 19 patients with affective disorders prior to lithium therapy (PLi).

The acute specific lesion was noted in all the Li patients' biopsies. A marked degree of distal tubular dilatation and microcyst formation was observed in biopsies of Li patients, compared to PLi patients ($p<.05$). Significant chronic renal damage was present in Li patients' biopsies when compared to cadaveric donor kidneys ($p<.001$), but similar damage was noted in PLi patients' biopsies and also differed from donor kidneys ($p<.01$). The degree of damage did not differ significantly between Li patients and PLi patients. Marked defects in urinary concentrating ability ($p<.001$) and urinary acidification ($p<.01$) were present in Li patients compared to PLi patients, but there was no evidence of a substantial reduction in glomerular filtration rate that could be ascribed to the lithium therapy.

CLINICAL SPECTRUM OF RHABDOMYOLYSIS. S. Kelleher,* G. Sachs,* W. Kaehny, P. Gabow. Denver Gen. Hosp. And Univ. Colorado Health Sciences Ctr., Denver, CO.

We reviewed 70 patients with rhabdomyolysis (CPK> 500 I. U. ±myoglobinuria) to define the frequency of clinical and laboratory abnormalities. Mean age of the patients was 48±17 yrs. 59 were male and 11 female. Risk factors included alcoholism in 58%, seizures in 36%, muscle compression in 36%, trauma in 31%, drug ingestion in 18%. Multiple factors were present in 70%. Mortality was 7%. 42% of patients had serum creatinine (Cr)≥4 mg/dL. 9 patients developed acute tubular necrosis (13%); 8 were oliguric. 7 oliguric and 1 nonoliguric patients required dialysis. 13% of patients had peak serum K values ≥6 mEq/L; 40% had peak P levels ≥7 mg/dL; 27% had peak uric acid (UA) values ≥12 mg/dL 37% had trough serum calcium (TCa) levels <7 mg/dL. The relationship between peak CPK and peak levels of these other serum constituents are presented below as mean ± SD:

CPK	N	Cr	K	P	UA
500-999	13	2.0±1.9	4.9±0.9	4.0±1.4	7.2±2.8
1000-9999	42	4.4±3.7	5.1±1.2	5.8±2.8	11.8±5.2
10000+	15	4.6±4.3	5.4±1.4	6.1±3.5	12.1±4.2

No correlation was found between CPK, K, P or UA. In contrast, abnormalities in these serum constituents were significantly more common in patients with peak Cr levels ≥4 mg/dL than in those with lower Cr ($P<0.01$ in all instances). TCa levels correlated with serum P but not with Cr or CPK. We conclude that 1) although an elevated Cr is common renal failure occurs in only 13% of patients 2) peak CPK levels less than 1000 predict few renal electrolyte abnormalities and 3) the degree of renal dysfunction appears to be more important than the level of CPK in producing biochemical abnormalities.

ABSTRACT RATING FOR THE 1979 ASN. DAVID W KNUTSON, and Jack W Coburn. VA Wadsworth Med. Ctr. and UCLA School of Medicine, Los Angeles, Calif. and Univ. of Rochester, Rochester, New York.

Selection of abstracts for presentation often has substantial consequences and involves effort and anxiety for submitters and selectors, alike. Last year, six Wadsworth nephrologists scored as many of the 326 Clinical Abstracts sent to a program committee member "as they felt comfortable rating" from 1 (best) to 5 (worst). (Mean # rated =261; range 208-300). An additional six academicians rated abstracts in their field of interest only. A single weighted mean score (of 5 to 9 scores) was then submitted to the Program Committee (PGC) who chose 126/326 abstracts for actual presentation. The "local" data were subsequently analyzed with a computer and the top 126 mean scores considered "accepted". Local "acceptance" correlated highly with PGC selection (68 accepted by both and 142 rejected by both, $p<.001$ by Chi square). However, there was disagreement on 58 abstracts or nearly half of the program. Profiles of the incidence of individual's scores varied widely. Raters mean scores (2.12-3.85) had no predictable impact on local "program selection". However, raters who gave a larger proportion of 1's and 2's (n=2) had more impact than raters whose scores centered around 3(n=3) or 4(n=1). We conclude: There is likely to be good agreement on >50% of the abstracts chosen for presentation and >80% of abstracts rejected regardless of who rates the abstracts or how the abstracts are selected from the scores. However, the selection of up to 40% of a program may depend on the system used and the idiosyncrasies of "high" and "low" raters. Normalization of scores may result in choices more representative of the program committee's true evaluation.

● ABSENCE OF METABOLIC BONE DISEASE IN ADULT PATIENTS WITH NEPHROTIC SYNDROME (NS) AND NORMAL RENAL FUNCTION (NRF). A. Korkor*, J. Schwartz*, M. Bergfeld*, S. Teitelbaum, L. Avioli, S. Klahr, and E. Slatopolsky. Washington University School of Medicine, St. Louis, MO.

Patients with NS and NRF have low levels of $25(OH)D_3$, presumably due to loss of this metabolite in the urine. Osteomalacia and hyperparathyroidism were recently reported to be a biologic consequence of this phenomenon. We studied five patients (age 26-49) with NS (mean duration 6.8 ± 3.7 years, range: 2-12 years) and NRF and evaluated their calcium, phosphorus, parathyroid hormone (PTH) and vitamin D metabolism. Bone biopsies were obtained in 4 patients. The creatinine clearance was 111 ± 25.6 (SD) ml/min, serum albumin 2.76 ± 0.36 gm/100 ml and proteinuria ranged from 3.5 to 13.2 gm/24 hr. All patients had normal serum magnesium, phosphorus, ionized calcium and alkaline phosphatase (bone fraction), and normal skeletal X-ray. Serum PTH measured by the C-terminal assay was 4.4 ± 1.67 µlEq/ml (normal 2-10), serum $25(OH)D_3$ was 10.1 ± 2.8 ng/ml (normal 15-30) and $24,25(OH)_2D_3$ was 3.2 ± 2.1 ng/ml (normal 3-6 ng/ml). The histologic appearance of all four biopsies were not different than a group of 17 similarly aged normal patients who died suddenly. Specifically there was no increase in the volume of osteoid, the percentage of trabecular surface covered by unmineralized bone matrix or in the number of osteoclasts. Thus, these data indicate that low levels of $25(OH)D_3$ in patients with NS and NRF do not necessarily result in the development of osteomalacia (as defined by the presence of excess osteoid due to delayed mineralization) or hyperparathyroidism.

PROSPECTIVE COMPARISON OF TOBRAMYCIN (T) AND GENTAMICIN (G) NEPHROTOXICITY AS MEASURED BY SHORT IOTHALAMATE CLEARANCE (C_I) VS. CREATININE CLEARANCE (Ccr), SERUM CREATININE (Scr) AND TUBULAR ENZYME EXCRETION. Stephen B. Kurtz, Thomas Keys,* and Donald Jones.* Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Using C_I as an accurate measurement of GFR we evaluated reliability of Scr, Ccr and urinary enzymes as markers of T and G nephrotoxicity in 27 patients with normal-stable renal function. Prospectively, 27 pts were entered alternatively into T group and G group. Scr, Ccr and urinary enzymes {N-acetyl glucosaminidase (NAG) and alanine aminopeptidase (AAP)} were obtained every other day. C_I was obtained pre and post treatment (0, 10 days). T and G serum levels were monitored every other day to assure peak levels <8 µg/ml and trough levels of 2 µg/ml or less.

Significant ↓ in C_I (>10%) occurred in 7/12 with T and 6/15 with G. Significant ↑ in Scr (>0.2 mg/dl) occurred in only 1/12 with T and 6/15 with G. Correlation of ↑ Scr/↓ C_I occurred in 1/7 with T and 3/6 with G. Significant ↓ in Ccr/↓ C_I occurred in only 2/7 with T and 3/6 with G. NAG and AAP rose in all patients, no correlation with ↑ Scr or ↓ C_I was found.

We conclude 1) that there is no difference between T and G toxicity as measured by GFR; 2) glomerular and tubular toxicity may be separate aminoglycoside effects; 3) measurement of Scr is a poor marker of toxicity; and, 4) urine enzymes lack clinical value.

REDUCED PARATHYROID RESPONSE TO ACUTE HYPOCALCEMIA IN DIALYSIS OSTEOMALACIA. J.A. Kraut, J.H. Shinaberger, F.R. Singer*, D.J. Sherrard, J. Saxton*, A.B. Hodsman*, J.H. Miller and J.W. Coburn. Depts. Med., VA Wadsworth Med. Ctr. and UCLA and USC Sch. Med., Los Angeles, CA.

Some dialysis patients develop a syndrome of osteomalacia (OM), a tendency toward hypercalcemia and low or normal parathyroid hormone (iPTH) levels. To determine if low iPTH levels occur via suppression by hypercalcemia, we measured serum (S) iPTH in response to an acute fall in SCa in 5 patients with OM and 4 other dialysis patients who served as controls (C). Parathyroid surgery had been done in 4/5 OM, but SCa was 9.6-11.4 mg/dl without vitamin D therapy. Measurements were made before and after 90 min of dialysis with dialysate Ca of 0 and then 120 min with dialysate Ca of 4.4 mg/dl. SiPTH was measured with a C-terminal antiserum. Predialysis SCa was higher (10.6±.3 vs 9.4±.3 mg/dl) and SiPTH lower (220±7 vs 1000±344 pg/ml; normal <400) in OM than C ($p<.05$). The fall in SCa at 90 min was greater in OM than C (-2.7±.2 vs -2.1±.2 mg/dl, $p<.05$). Despite a greater fall in SCa, SiPTH levels were unchanged in OM but rose in C (ΔSiPTH,+43±36 vs +523±108 pg/ml in OM and C, respectively). Thus, SiPTH levels failed to respond to hypocalcemia in OM, data suggesting that low SiPTH levels are not caused by hypercalcemia but may arise from parathyroid failure. The greater fall in SCa during hypocalcemic dialysis suggests that the miscible pool of Ca is smaller in OM than C. Both the possible role of low iPTH in the pathogenesis of OM and the mechanism for the maintenance of normal or high SCa in dialysis patients with restricted parathyroid responsiveness are uncertain.

● SENSITIVITY OF URINARY ACIDIFICATION INDICES (UAI) IN ASSESSING IMPAIRED DISTAL ACIDIFICATION (DA) AS SHOWN BY THE EFFECT OF Li THERAPY. N.A. Kurtzman, D.C. Batlle, M. Gaviria,* M.Grup,* and J.A.L. Arruda. Univ. of ILL. Hospital, Chicago, ILL.

Therapeutic (T) Li levels are said to cause incomplete distal renal tubular acidosis (DRTA). We studied the effect of T levels of Li on DA by the systematic evaluation of UAI in seven patients with normal GFR and impaired concentrating capacity (CC) (U max 675±58 mOsm/kg H_2O). Attempts to use the urine-blood (U-B) pCO_2 as a UAI have not taken into account the presence of impaired CC which limits the generation of high urine (U) (HCO_3) in Li treated patients. The maximal U-B pCO_2 after $NaHCO_3$ loading, was markedly reduced as compared to controls (3.7±5.4 vs 41.2±5.5 mmHg, $p< 0.01$) at comparable U(HCO_3). The maximal UpH achieved during $NaHCO_3$ loading was higher in Li treated patients than in controls (8.04±0.03 vs 7.84±0.02, $p<0.01$). Thus, the inability of Li treated patients to raise the U-B pCO_2 despite adequate U(HCO_3) was the result of impaired DA rather than impaired CC. Neutral phosphate infusion resulted in a normal increase in U-B pCO_2 in all patients (53±3.2 mmHg). None of the patients were acidotic and all were able to lower the UpH below 5.3 (5.1±0.06) in response to a 3 day NH_4Cl loading test. Thus, T levels of Li cause a mild DA defect that can only be disclosed by measurement of the U-B pCO_2 in maximally alkaline urine. Under these conditions, the pH gradient for H^+ secretion is favorable but the homeostatic need for H^+ secretion is absent. The UB pCO_2 during HCO_3 loading provides a very sensitive tool to assess the integrity of DA; failure to generate a pCO_2 gradient may be the earliest detectable abnormality in DRTA.

DISTURBANCES IN THE FUNCTION OF THE HYPOTHALAMIC-PITUITARY GONADAL (H-P-G) AXIS DURING ACUTE RENAL FAILURE (ARF) IN THE MALE. D. Levitan, S. Moser,* D.A. Goldstein, O. Kletzky,* and S.G. Massry. Div. Neph., Dept. Med. and OBGYN, USC Sch. Medicine, Los Angeles, CA.

Chronic uremia is associated with abnormalities in the serum levels of testosterone (T), FSH, LH and prolactin (Prl), and parathyroid hormone (PTH) stimulates release of Prl in normal subjects. ARF is associated with uremia and hyperparathyroidism. Therefore, we examined whether ARF is associated with abnormalities in the serum levels of these hormones. Twenty patients with ARF of various etiologies were studied. In these 20 patients serum T (2.1±.42 ng/ml) and FSH (1.4±.16 m/U/ml) were significantly ($p<0.01$) lower than values obtained in 60 normal subjects (T:8.8±.41 ng/ml and FSH:3.0±.41 m/U/ml), while serum Prl (33.3±4.9 ng/ml) was significantly higher than normal (7.8±0.6 ng/ml). Serum PTH (247±54 µlEq/ml) was elevated (normal <µl0 µlEq/ml). There was a direct and significant correlation between serum Prl and PTH ($r=.58$, $p<0.01$). Changes in serum LH were not consistent. With recovery of ARF the serum levels of hormones normalized. The responses of serum FSH, LH and Prl to GnRH and TRH were abnormal in most of the six patients studied during ARF and the response normalized after recovery of renal function. The results suggested that: 1) ARF, per se, produces marked abnormalities in the function of the H-P-G axis, 2) secondary hyperparathyroidism in ARF may be partly responsible for the rise in serum Prl, and 3) deficiency of endogenous GnRH or resistance to its action may be present in ARF and may contribute to the low FSH.

ACUTE INTERSTITIAL NEPHRITIS DUE TO DRUGS. Adam L. Linton, William F. Clark and Robert M. Lindsay. Section of Nephrology, Victoria Hospital and The University of Western Ontario, London, Canada.

Nine cases of acute interstitial nephritis (AIN) due to drugs were identified by renal biopsy over a period of 1 year. All presented as otherwise unexplained acute renal failure, and constituted 8 percent of all cases of acute renal failure seen. Drugs implicated included ampicillin, sulfonamides, sulfinpyrazone, ibuprofen and hydrochlorothiazide. Diagnosis may be suggested clinically by coincident pyrexia, skin rashes or arthralgias, but this triad occurs only in about 15 percent of cases. Duration of exposure to drug varied from 5 to 26 days, and in all cases renal function deteriorated rapidly, with oliguria in 7 of the 9 patients. Urinary indices were of little value in diagnosis, and macroscopic hematuria seldom occurred. Eosinophils were identified in the urine in 6 of 9 patients, although late in the course of the disease in 2. Raised blood eosinophil counts and elevated serum IgE levels were found in 6 of 9 patients, and Ga^{67} scanning revealed intense uptake of the isotope in all 9 patients with AIN, contrasted with minimal or no Ga^{67} uptake in 6 cases of vasomotor nephropathy. In 2 cases of AIN evidence of complicating renal papillary necrosis was found. All 9 cases recovered to near normal renal function coincident with administration of steroids; only 1 required hemodialysis. AIN may be more common and more difficult to diagnose than is presently believed.

EFFECTS OF PROSTAGLANDIN INHIBITION ON PROTEIN EXCRETION AND RENAL HEMODYNAMICS IN PATIENTS WITH PROTEINURIA. E. Lianos*, N. Alavi*, R. Venuto, J. Brentjens and C. Bentzel. Dept. of Medicine, SUNY at Buffalo, N.Y..

Acute (60 min) and long term (5 day) effects of Indomethacin (INDO) were evaluated in 6 proteinuric patients (Pts) with a variety of glomerular diseases. Changes in protein excretion and renal hemodynamic parameters resulting from prostaglandin (PG) blockade were measured in each individual during volume expansion (↑VOL: 200 meq Na diet) and during volume depletion (↓VOL: 20 meq Na diet and hydrochlorothiazide 50 mg twice daily). Under ↓VOL INDO decreased GFR (C_{IN} ml/min), RPF (C_{PAH}, ml/min), $U_{PROT}V$ mg/min) and $U_{PGE_2}V$ (pg/min) 60 min after PO administration. These effects were attenuated when INDO was given under ↑VOL:

* p 0.05	↓ VOL		↑VOL	
	PRE(I)	POST(I)	PRE(I)	POST(I)
GFR	52±13	33±8*	49±12	39±10*
RBF	293±39	153±26*	366±33	277±27*
$U_{PROT}V$	6.1±1.5	3±0.8*	7.2±1.5	7.1±1.4
$U_{PGE_2}V$	542±244	210±105*	152±65	110±53*

PG synthesis was increased during ↓VOL. INDO 150 mg daily for 5 days decreased GFR (C_{CREAT}) and 24 h U_{PROT} by 18% and 47.5% respectively. This effect occured only during ↓VOL.

We conclude: a) INDO reduces proteinuria both acutely and chronically. b) INDO reduces protein excretion more than can be accounted for by the decrement in GFR. c) This effect of INDO appears to require the heightened PG synthesis seen in ↓ VOL.

CLINICAL VALUE OF THE RENAL BIOPSY(RB) IN ADULTS OVER 50 YEARS OF AGE. L.Mailloux, M.Susin,P.Bluestone,R.Mossey,and K.Hurst, North Shore University Hosp.,Division of Nephrology, Manhasset, N.Y.

Sixty RB's were performed in 30 males and 30 females over the age of 50 for primary renal disease; patients (PT) with known systemic disease were excluded from this evaluation.These 60 pts represented 20% of the total adults undergoing RB during the 9 yr. period of study.There was 1 major complication(1.6%) with persistent hemorrhage in an azotemic hypertensive pt. Indications for biopsy were the nephrotic syndrome(NS) 35, hematuria and/or proteinuria 14, and renal insufficiency 11. The pathologic diagnoses were focal glomerulosclerosis(FGS) 27%, membranous nephropathy (MGN) 17%, minimal change disease(NIL)13%, amyloid 10%, membranoproliferative glomerulonephritis 7%, tubulointerstitial nephritis 5%, crescentic nephritis 3%,diffuse proliferative nephritis 3%, and other nephropathies 15%. The diagnosis of NIL was made in 7 of 35 pts with NS: all obtained a prolonged remission with steroid alone.The NS was present in 50% of 16 pts with FGS, either global or segmental. Patients with FGS do not respond to steroids and have a considerably poorer prognosis than others with NS in this age group.The RB is a safe and useful diagnostic tool in pts over the age of 50 identifying those who have steroid responsive lesions, an important therapeutic consideration in these pts.

URINARY CITRATE AND CALCIUM EXCRETION AND NEPHROCALCINOSIS IN NON-AZOTEMIC TYPE 4 RTA. E. McSherry, J. Gates*, M. Pialaet*, UCSF, San Francisco, CA

In children with Type 1 RTA, despite low-dose (1-3 meq/kg/d) alkali therapy since infancy, invariably Nephrocalcinosis (NC) occurs by age 4 yrs and $U_{CIT}V$ (urinary citrate excretion) is low. With high-dose (5-14 meq/kg/d) alkali, $U_{CIT}V$ normalized in each of 10 children with Type 1 RTA; in the 7 of 10 in whom correction of both acidosis and hypocitraturia was sustained from infancy, NC and NL (nephrolithiasis) did not occur over 10-20 yrs. We evaluated $U_{CIT}V$, $U_{CA}V$, and the occurrence of NC and NL, in 14 children, 9 boys and 5 girls, ages 2 mo. to 4 yrs., with non-azotemic Type 4 RTA. In paired metabolic studies on fixed normal diet, during acidosis, $/HCO_3^-/p$ 19.8±2.4 mEq/L, mean $U_{CIT}V$ in girls was 559±307 (normal 300-1800), in boys, 529±196 mg/1.73 M^2/d (normal 250-1750). After 3-6 mos. sustained correction of acidosis, $U_{CIT}V$ was 1437±550 for girls; for boys, 1437±550 mg/1.73 M^2/d. The means for the entire group of 14 before and after correction of acidosis were 530 and 1572, respectively ($p < 0.005$). During acidosis, citrate is normally completely reabsorbed by the proximal and distal tubules. $U_{CIT}V$ is low or unmeasurable during acidosis in normal children or those with Type 1 RTA. In children with Type 2 RTA and Fanconi syndrome, $U_{CIT}V$ is high during acidosis, and NC and NL do not occur. Radiologically demonstrable NC and NL did not occur in any of the 14 children with non-azotemic Type 4 RTA, including 5 who were acidotic 2-4 yrs. In these patients $U_{CA}V$ did not rise significantly with acidosis. In patients with non-azotemic Type 4 RTA, the absence of NC and NL may be due in part to abnormalities in the renal handling of calcium and citrate during acidosis.

TUBULAR BLOCKADE BY COMBINED DIURETIC THERAPY IN END STAGE RENAL FAILURE. A. Meyrier, K.S. Ang and P. Simon (introduced by G.S. Hill), Hôpital Tenon, Paris, France.

Adaptive mechanisms which preserve sodium balance in chronic renal failure are no longer efficient in patients (pts) with extremely reduced GFRs, especially in those who undergo intermittent hemodialysis (HD). Furosemide has long been utilized in high dosage to increase Na^+ excretion in such pts, but this thick ascending limb diuretic is incapable of achieving sufficient tubular blockade. We therefore decided to test the effect of combination diuretic therapy on Na^+ balance in end stage renal failure. Ten pts with GFRs of 7.5 to 0.6 ml/min (8 of whom were treated by HD) were studied during 5 consecutive 2-week periods (P) : P1: steady state; P2: furosemide (F), 500 mg; P3: F + chlortalidone (C), 100 mg; P4: F + C + [Amiloride, 5 mg + Hydrochlorothiazide, 50 mg] (M); P5: F + C + M + Acetazolamide, 250 mg. Body weight was maintained stable throughout the study by adjusting Na intake. Results : The Na output increased stepwise from one period to another. The Na/creatinine ratio was (m ± SD): P1 = 15.3 ± 8.8; P2 = 18.2 ± 15 ($p < 0.01$); P3 = 24.3 ± 18 ($p < 0.01$); P4 = 46 ± 36 ($p < 0.05$); P5 = 51 ± 9 (ns). The average 24 hr Na excretion increment from P1 to P4 or P5 was × 1.59 to × 6.93 ($p < 0.02$ to $p < 0.0001$). In 2 pts the improvement of urinary output and Na balance was such as to allow withdrawal from HD. Conclusions : (1) the renal tubule remains sensitive to diuretics whatever the degree of nephronic reduction; (2) Diuretics with different sites of action exert cumulative effects on Na reabsorption in CRF; (3) Tubular blockade has a definite clinical usefulness in CRF and HD.

GLYCOSYLATED HEMOGLOBIN MEASUREMENTS IN DIABETIC AND NON-DIABETIC CHRONIC RENAL FAILURE. P.K. Mehta, R.A.Kienstra, S.Mitra C.C.Maher, R.T.Bilinsky, Memorial Med.Ctr. Dept. of Med., S.I.U. School of Medicine, Springfield, Illinois.

Both elevated and low levels of glycosylated hemoglobin (HbA_1) are reported in patients with chronic renal failure (CRF). Whether HbA_1 measurements can assess the glycemic control in diabetics with CRF and on dialysis is not clear. Nonfasting plasma glucose(PG) was measured monthly for 3 months. At the end of 2 months HbA_1 was measured by microcolumn chromatography. 5 groups were compared. Group 1: 20 normal subjects. Group 2: 20 CRF patients. Group 3: 20 CRF patients on dialysis. Group 4: 8 diabetic CRF patients. Group 5: 17 diabetic CRF patients on dialysis. In dialysis patients samples were drawn on non-dialysis days. Values are expressed as mean±SD.

Group	PG(mg/dl)	HbA_1(%)	HbA_1 Range
1	87±10	5.4±0.7	4.2- 6.6
2	105±17	6.5±1.6	4.1- 8.9
3	107±16	6.6±1.4	4.4- 9.0
4	237±107	10.3±3.8	5.9-16.8
5	247±127	9.3±2.8	4.2-15.2

In diabetics, Group 4 and 5, PG and HbA_1 were significantly greater than Group 1,2and 3,($p<.01$) and there was a positive correlation of HbA_1 with PG($r=.8$). In non diabetic CRF, Group 2 and 3, HbA_1 and PG values were also significantly higher than normal subjects,($p<.02$) and there was poor correlation of HbA_1 with PG ($r=.4$).

Conclusion: 1) HbA_1 assay is a useful test to assess glycemic control in diabetic CRF. 2) HbA_1 is elevated in patients with non diabetic CRF and does not correlate with PG. 3) HbA_1 measurements cannot be used with certainty to discern diabetic patients from non diabetic in the presence of CRF.

ACUTE INTERSTITIAL NEPHRITIS ASSOCIATED WITH NON-STEROIDAL ANTI-INFLAMMATORY AGENTS. Sheila Moriber Katz*, Ralph Capaldo and Paul Bosanac, Hahnemann Medical College and Hospital, Philadelphia, Penna.

We have previously linked phenoprofen and naproxen, nonsteroidal anti-inflammatory agents (NSAIA) derived from proprionic acid, to nephrotic syndrome, reversible renal failure and acute interstitial nephritis (AIN) (Brezin et al, N Engl J Med, 301: 1271-1273, 1979). A 70 year old woman developed reversible renal failure and acute interstitial nephritis while ingesting tolmetin sodium, a NSAIA derived from acetic acid. The patient had peripheral eosinophilia. oliguria, proteinuria and eosinophilia. Admission serum creatinine was 11 mg/dl. A renal biopsy on day 7 disclosed acute allergic interstitial nephritis. By light microscopy, there was an interstitial infiltrate of eosinophils, plasma cells, histiocytes and lymphocytes. By immunofluorescence microscopy, deposits of immunoglobulins, complement and fibrinogen were present in interstitial tissue and tubular basement membranes. By electron microscopy, only 15% of glomerular foot processes were effaced. Medications were discontinued on admission and prednisone initiated on day 8. 7 weeks after admission, serum creatinine was 1.4 mg/dl and peripheral eosinophilia was absent. A second patient, also treated with tolmetin sodium, had clinical and pathologic findings similar to the case detailed herein, but the AIN was superimposed on penicillamine-associated segmental membranous nephropathy. Therefore, tolmetin sodium may be related to reversible renal failure and AIN that differs in some ways from renal findings attributed to other NSAIA.

THE LOW INCIDENCE OF PULMONARY EMBOLISM IN CHRONIC RENAL FAILURE (CRF), R.Mossey, L.Mailloux, P.Bluestone, B.Wilkes*, and A.Kasabian*, North Shore Univ. Hosp., Div. of Nephrology, Manhasset, N.Y.

The autopsy reports of all adult patients (>18 yrs) for the years 1969 through 1979 inclusive were reviewed for the presence of pulmonary emboli. There were 2,255 adult autopsies performed during this interval. Microscopic emboli were detected in 18.5%;4% had major emboli and 9.9% had both major and microscopic evidence of pulmonary emboli for an overall incidence of 32.4%.There was no correlation with the presence of arteriosclerotic heart disease, congestive heart failure or cancer;however, there was a strong positive correlation with age (r=0.951, p<.001).At the same time, 84 cases of CRF (creatinine>5.0mg%) were identified. In this group, 9 microscopic emboli were detected (10.7%).There were no major emboli detected and in no case were the emboli the cause of death. There was no correlation with arteriosclerotic heart disease, congestive heart failure, cancer, or age. There was a substantial difference in incidence when compared to the overall population(p<.001).Our data support the clinical impression that CRF is associated with a marked reduction in the incidence of life-threatening and minor pulmonary emboli.We conclude that pulmonary embolism is an infrequent cause of morbidity in patients with CRF.

● CYST FLUID ANTIBIOTIC LEVELS IN POLYCYSTIC KIDNEY DISEASE (PCKD): DIFFERENCES IN PROXIMAL AND DISTAL CYST PERMEABILITY. Richard S. Muther, and William M. Bennett, Univ. of Oregon Hlth. Sci. Ctr., Div. of Nephrol., Portland, Oregon.

Cyst fluid concentrations (CFC) of several antibiotics were measured in six patients with PCKD. 101 cysts (70 proximal and 31 distal) were aspirated at surgery or autopsy. Proximal and distal cysts were differentiated by cyst fluid to serum sodium ratio. Cyst volumes were 1-967 ml (mean 10.3 ml). Serum, urine and cyst fluid were simultaneously analyzed for sodium, creatinine, gentamicin, tobramycin, cephapirin and ticarcillin. Five patients had severe renal failure. In one patient with a creatinine clearance (Ccr) of 105 ml/min, inulin and para-aminohippurate (PAH) were infused for 36 hours prior to cyst sampling.

Antibiotics were either undetectable or present in low concentrations in renal cysts. Concentrations did not correlate with either cyst volume or Ccr. Data for individual drugs reveal:

Drug	# Pts	Serum	Urine	CFC:Proximal	CFC:Distal
Genta.	3	2.9	11	1.04 (19)	0 (14)
Tobra.	2	3.7	28	0 (2)	0 (3)
Ceph.	3	46	448	8.1 (42)	38 (1)
Ticar.	1	400	--	135 (7)	0 (13)

( ) = # of cysts sampled; concentrations in µg/ml

In the patient with normal renal function, inulin was not detected in any cyst while [PAH] was 25% of serum values. These data explain the poor response of infected renal cysts to antibiotics. They also imply that cyst fluid composition relates to tubular cell function/surface area rather than glomerular filtration. Proximal and distal cysts appear to manifest qualitative differences in permeability.

URINE AND SERUM LACTIC DEHYDROGENASE (LDH), LDH ISOENZYMES AND ALKALINE PHOSPHATASE (AP) IN NEPHROTIC SYNDROME (NS). Charles B. Murdock,* Patricia J. Baker,* Elizabeth DeLong,* Charles R. Roe,* Stephen G. Osofsky. Duke Univ. Med. Ctr., Dept. of Ped. & Comm. and Fam. Med., Durham, N.C.

Urinary and serum LDH, LDH isoenzymes and AP levels were determined for children with known NS (N=31) as well as normal controls (N=35 urine, N=56 serum). Patients with NS were grouped as to being in relapse, remission without prednisone, remission for > 21 days receiving prednisone, or remission for < 21 days receiving prednisone. The relapse group had significant elevations of urinary LDH and AP when compared to each of the other groups. The highest urinary LDH values were seen in the relapse group, and the lowest in normals. The groups in remission had intermediate values of urinary LDH which decreased as the length of time in remission increased. Although urinary AP levels were elevated in relapse, patients in remission > 21 days receiving prednisone had subnormal AP activity suggesting membrane stabilization with resultant reduction in enzyme release into the urinary tract. The urinary and serum LDH isoenzyme patterns in the relapse group did not resemble each other indicating the increased urinary activity was not solely due to renal clearance of serum enzymes. Serum LDH was elevated in relapse (p <.01) but the remission group was no longer statistically different from controls. This study demonstrates increased urinary LDH, AP and serum LDH activity in patients with the relapsed NS. In relapsed patients the different serum and urine LDH isoenzyme patterns suggests that the urinary activity may be derived from diseased renal tissue.

● DYNAMICS OF GLOMERULAR FILTRATION FOLLOWING OPEN CARDIAC SURGERY. Bryan D. Myers, Brian J. Carrie*, Mark Hilberman*, Channing R. Robertson*, Stanford University, Stanford, California.

To determine if factors other than a diminished renal plasma flow (RPF) play a role in the reduced glomerular filtration rate (GFR) observed with low output cardiac failure (CF), 34 sodium-retaining patients were studied 1 to 4 days following cardiac surgery. Patients who remained non-azotemic (n=17, Group I) were compared with those who became azotemic (n=17, Group II). Clearances of inulin (GFR), PAH (RPF), fractional clearance of dextran 40 (Θ_{dex}) and afferent oncotic pressure (π_A) were determined. Efferent π (π_E) was calculated from filtration fraction. Results (mean±SE) were, *p<.02:

	Stroke work $g\cdot m/m^2$	RPF $ml/min/1.73m^2$	GFR	π_A	π_E
				---mmHg---	
Group I	28±3	317±22	76±6	21±2	33±1
Group II	14±2*	152±26*	21±2*	21±1	29±1*

GFR correlated with cardiac index in Group I (r=.69) but not in Group II (r=.30). Failure of GFR to change over a 24-hour period despite increases in RPF (32% Group I, 23% Group II) suggested that both groups were at filtration pressure dysequilibrium (FPD) thereby permitting a unique filtration coefficient, Kf, to be calculated. Over a range of values for transglomerular hydraulic pressure (ΔP) such that $3 \leq (\Delta P - \pi_E) \leq 10$mmHg (to simulate FPD) Kf >0.07 (Group I) but <0.07 $nl\cdot sec^{-1}\cdot mmHg^{-1}$ (Group II). Elevation of Θ_{dex} (radii 30-40Å) in Group II vs. Group I indicated that Kf reduction was insufficient to offset the effects of reduced RPF on transglomerular dextran sieving. We suggest that hemodynamic factors alone appear to regulate GFR when CF is mild, but low Kf contributes to GFR reduction when CF is severe.

EVIDENCE FOR A RENAL CALCIUM (Ca) LEAK IN HYPERCALCIURIC (HC) PATIENTS. L. Nascimento, F. Oliveros,* and E. Cunningham*. Veterans Hospital, Univ. of Puerto Rico, San Juan, Puerto Rico.

We evaluated the renal handling of Ca in normal (N) subjects (n=4) and HC patients (n=12) during different states of salt intake (outpatient home diet, normal diet-190 mEq of Na and Low salt diet-35 mEq of Na as inpatients). Calcium intake was kept unchanged. Following a low salt intake significant weight losses were observed in both groups (4 vs 4.2 lbs). The average Ca (UCaV) and Na (UNaV) excretions were significantly lower on normal diet than on the outpatient regimen. The HC patients significantly decreased UNaV, UCaV and fractional excretions of Na (FeNa) and Ca (FeCa) following salt restriction. GFR were comparable in N and HC. Two distinct responses were elicited by HC patients: a) 4 patients (group I) responded similarly to N; UCaV were under 100 mg/day when UNaV were equal or less than 50 mEq/day; for FeNa of 0.4% or less the values for FeCa were equal or less than 1%, b) in 8 patients (group II) a significant renal Ca leak was detected; UCaV were above 120 mg/day (range 120-290) when UNaV were under 50 mEq/day; FeCa were above 1.3% (range 1.3-4.8) corresponding to FeNa of 0.4% or less. Conversely in N subjects UCaV ranged from 30 to 80 mg/day for similar UNaV; FeCa were 1.2% or less for FeNa of 0.4% or less. These differences were highly significant. Parathyroid hormone (PTH) levels were normal in these patients. These results show that: 1) a renal Ca leak was clearly demonstrated during low salt intake in HC patients, b) a few patients showed a similar response to the N, c) PTH cannot account for this difference since serum levels were normal.

ANEPHIC (A) PATIENTS ON DIALYSIS OVER TEN YEARS. THE CLINICAL PROFILE AND PROTECTIVE ROLE OF HYPOTENSION. Abe Pahilan*, A. Gan, M. M. Avram, The Long Island College Hospital, Division of Nephrology, Department of Medicine, Brooklyn, New York.

To further understand the pathophysiology of binephrectomized long-term survival on hemodialysis, we compared the data of patients with surgically extirpated kidneys with that of their nephric counterparts (N) who started maintenance dialysis together between 1968-70.

There were 6 A patients of 158 started that period (4.4%). Prenephrectomy diagnoses were: 3 malignant uncontrollable hypertension, 1 systemic lupus, 1 post-partum necrosis with hypertension, 1 transplant nephrectomies. The A group started dialysis at mean age 24.7±11.2 years, versus N group 42.4±10.9 years. In the A group there were 5 females (83.3%) all still irregularly menstruating and 1 male (16.7%) versus 61% female and 49% males in the N group. Race distribution of A group, 5 black (83.3%) and 1 hispanic (16.7%).

Interestingly, the mean systolic blood pressure of the A group was 92.8±18.1 and diastolic 56.4±12.1 versus N group systolic pressure of 122.2±23.3 and diastolic 74.2±1 ($p<0.5$). The mean hematocrit (Hct) of the A group was 18.67±2.1% versus mean Hct on N group of 24.6±3.4% ($p<0.5$).

This data infers that binephrectomized patients over 10 years on dialysis are younger, predominantly menstruating females and black, and have significantly lower systolic and diastolic systemic blood pressures and lower Hcts than their nephric counterparts. A protective role for hypotension, with lower Hct no barrier to survival, is suggested by this data.

ESSENTIAL SPORADIC OSTEOLYSIS WITH END-STAGE RENAL DISEASE (ESRD) ON CHRONIC MAINTENANCE HEMODIALYSIS. J. Dennis North-Coombes, Wm. C. Kendrick, Jr., Greenville Nephrology Associates, Greenville, South Carolina.

We present here a 57 year old black female who presented in October of 1979 with endstage renal disease.

She was found to have clinical and radiological features typical of essential sporadic osteolysis affecting the carpal and tarsal bones. The latest report in the literature (W.M. Bennett, et al, Nephron 25: 134-138) describes the 9th case of essential sporadic osteolysis with renal involvement. The first renal manifestations are those of albuminuria followed by hypertension. The onset of renal involvement varies from 2 to 18 years. The renal histology in autopsied or biopsied cases reveals changes compatible with chronic glomerulonephritis and/or arteriosclerosis. The oldest patient died at age 22 of renal failure (Marie et al, Presse Medicale 71: 249, 1963). Our patient is the 10th patient and she is the oldest by far at age 57 and the first patient to be on chronic hemodialysis. Because of the short forearms, access placement was difficult. She is being dialyzed through a bovine graft in the left upper arm. She remains stable on maintenance hemodialysis.

● HLA Bw35 ANTIGEN AS A MARKER FOR SEGMENTAL SCLEROSIS AND PROGRESSIVE DISEASE IN IgA MESANGIAL GLOMERULONEPHRITIS (MGN-A). V. Pardo*, T. Pardo, A. Clerch, J. Strauss*, and V. Esquenazi. VAMC and Departments of Pathology, Surgery, & Pediatrics, University of Miami School of Medicine, Miami, FL.

Familial instances of mesangial IgA glomerulonephritis (MGN-A) suggest a genetic influence in the etiopathogenesis of the disease. We compared the distribution of HLA A,B, and C antigens in 21 cases of MGN-A and 524 healthy controls. There was a significant increase in Bw35 frequency in these patients (46% vs. 23% in controls; $p<0.01$). The Dr7 antigen was also associated with the disease contrasting the findings in 17 patients investigated and 96 controls (43% vs. 18% in controls).

While SIgA peripheral blood lymphocytes were increased in MGN-A (means: 12% patients vs. 5% controls) there were no differences in serum immunoglobulins levels.

We observed an increased incidence of segmental glomerular sclerosis and proliferation in the biopsies of the Bw35 positive patients (9/10 vs. 5/11 in the Bw35 negative group; $p<0.001$). Three cases in this Bw35+ subgroup developed renal failure 3 - 5 years post-biopsy. The histologic finding of segmental sclerosis was associated with higher mean age and urinary protein excretion. The HLA Bw35 antigen may represent a marker (risk to be diseased=10) to facilitate the identification of instances of MGN-A that develop progressive glomerular sclerosis and renal failure as well as an indication for kidney biopsy in the presence of recurrent primary hematuria.

LONG TERM EFFECT OF CHLORAMBUCIL IN NEPROTIC SYNDROME OF CHILDHOOD. José F. Pascual, Mary Molina,* and Julie López.* San Juan City Hospital and Univ. of Puerto Rico School of Medicine, Pediatric Nephrology Div., San Juan, P. R.

The long term effect of Chlorambucil (C) was observed in 35 children who did not respond adequately to steroids. C 0.2 mg/kg/day was given for 90 days with prednisone (P) 40 mg/24 hr./m^2 on 3 consecutive days out of 7 to children with frequently-relapsing nephrotic syndrome (FRNS) or with steroid-resistant nephrotic syndrome (SRNS). Twenty-two children were followed for 7 to 99 mos. (mean 48 mos.) after receiving C. All 22 children became protein-free; 12 have continued in remission for an average of 35 mos. (range, 7-67 mos.), and 10 had 1 to 9 relapses (average, 4.2) in 26 to 99 mos. (average, 62.4 mos.). Thirteen children with SRNS were followed for 5 to 90 mos. (mean, 53 mos.). Six children had a complete remission; 3 of them have had no relapses in 90, 78, and 32 mos. Three had a complete remission, but relapsed after 41, 17, and 5 mos. Another 3 failed to go into remission. Four had a partial remission. Complications were leukopenia (11), anemia (5), bacterial infections (3), and increased hair shedding (4). Viral infections, seizures, leukemia, solid tumors, nor death were observed. The results suggests that that C was effective in preventing relapses and prolonging remissions in FRNS. It was also effective in producing a remission in children with SRNS. Because of its potential toxicity, the use of C should be limited to children with serious steroid toxicity and those with SRNS.

VALUE OF IMMUNOGLOBULIN DEPOSITION IN THE SKIN IN DISTINGUISHING LUPUS NEPHRITIS FROM OTHER RENAL DISEASES. T.K.S. Rao, C. Levitz,* L. Pertschuk,* A.D. Nicastri, E.A. Friedman. Downstate Medical Center, Brooklyn, New York.

We studied the correlation between immunoglobulin deposition in skin biopsies obtained from an apparently normal forearm with that of simultaneously obtained percutaneous renal biopsies in 54 patients with various renal diseases seen over two years. In 20 patients with systemic lupus erythematosus (SLE) and renal involvement (mesangial in 1, focal in 6, membranous in 8, diffuse proliferative in 5), 13 (65%) showed deposits of IgG, IgM, IgA, or C_3 at the dermal epidermal junction. All of 5 SLE patients with diffuse proliferative nephritis had immune deposits in the skin. In 34 patients with other types of renal disease (lipoid nephrosis in 2, focal sclerosis in 7, membranous GN in 6, crescertic GN in 5, membranoproliferative GN in 1, post streptococcal GN in 1, mesangial proliferative in 1, focal GN in 1, Berger's disease in 3, other miscellaneous in 7), only one had deposits of IgG and C_3 in skin.

From these findings we infer that immunoglobulin deposition in skin (present in 65% of patients with SLE and in 100% of those with diffuse proliferative lesion) is a valuable aid in distinguishing patients with SLE (in whom renal biopsy cannot be performed) from other forms of renal disease.

FIBRINOLYTIC ENZYME INDUCED LYSIS OF OCCLUSIVE RENAL PELVIC BLOOD CLOT. Rajendra Pradhan, Alexios Dimas.* Cabrini Medical Center, Department of Medicine, New York, N.Y.

Instrumentation induced ureteric trauma may cause urinary obstruction due to spasm, edema and blood clot. This report describes lysis of occlusive blood clot by instillation of fibrinolytic enzymes. A 60-year old man developed hematuria, severe oliguria and renal failure following withdrawal of retrograde ureteric catheters which were previously inserted to avoid ureteric injury during resection of cancerous colon. Iatrogenic perforation of lower part of Rt. ureter had occurred during retrograde catheterization. Lt. ureter alone was recatheterized on 4th post op. day. Brisk urinary drainage ensued from Lt. ureteral catheter. Lt. retrograde pyelogram showed the tip of ureteric catheter to be situated past a fairly large filling defect caused by renal pelvic blood clot occluding the ureter. 20,000 U of streptokinase and 5000 U of streptodarnase were instilled 4 hourly via the Lt. ureteric catheter. Three days later (7th post op. day), a repeat retrograde pyelogram revealed dissolution of clot. Enzymes were discontinued. Lt. uretric catheter was withdrawn 4 days later (11th post op. day). The urinary outflow from the Rt. ureter resumed on reinsertion of catheter on the 7th post op. day and continued to maintain good drainage on removal of catheter on 14th post op. day. A renal sonogram done on 14th post op. day revealed no abnormality.

EFFECT OF CORONARY ANGIOGRAPHY (CA) ON RENAL FUNCTION IN DIABETIC NEPHROPATHY (DN). Caryl Richards,* Donald Steinmuller, Daniel Phillips,* William Braun, Andrew Novick, and Carol Buszta.* Cleveland Clinic Foundation, Cleveland, Ohio

Previous reports have suggested that intravascular administration of contrast agents can precipitate irreversible renal failure in patients with DN and renal insufficiency. In order to assess the risk of CA in these patients, we retrospectively reviewed the change in serum creatinine (C) in 24 patients with DN not yet requiring regular dialysis. CA was performed as part of our routine kidney transplant evaluation. All the patients had insulin dependent diabetes mellitus, diabetic retinopathy, proteinuria, and progressive renal insufficiency compatible with DN. CA was performed with a minimal amount of contrast, and volume depletion and other contrast studies were avoided if possible before and after CA. The C before CA ranged from 4.1 to 16 mg%. Fourteen patients had no significant ($<10\%$) permanent change in C after CA (mean change $0.0 \pm .2$ mg%). Most of these patients had a transient elevation of C (mean maximum change $1.0 \pm .3$ mg%) 2 to 7 days post CA. Seven patients did not have sequential measurement of C and the reversibility of any change in C could not be assessed. However, none of these patients required dialysis within 2 months of CA. Three patients had an increase in C not entirely reversible or partially responsible for the onset of dialysis. The change in C was 1.3, 1.2, and 2.5 mg% for these three patients. It is concluded that CA can be performed with minimal permanent effect on renal function in patients with DN not yet on dialysis.

LONG-TERM (11-12 YEARS) PROGNOSIS OF EPIDEMIC POST-STREPTOCOCCAL GLOMERULONEPHRITIS (EPSGN). Bernardo Rodríguez-Iturbe,* Rafael A. García, and Lírimo Rubio *. Renal Service, Dpt. of Med., Hospital Universitario and Universidad del Zulia, Maracaibo, Venezuela.

In 1968 there was an outbreak of 384 cases of EPSGN in Maracaibo. Of them, 120 cases were recalled in 1974 and reported previously. The present work concerns 71 patients from this group followed for 11-12 years and studied with creatinine clearance (C_{Cr}), proteinuria and urine sediment analyses. Determinations of Igs, cryoglobulins, C3 levels and rheumatoid factor were also done.

One patient developed uremia and is in chronic dialysis. Persistent abnormalities were detected in 21.1% of the patients. Depressed C_{Cr} was found in 12.6% of the patients and proteinuria (0.5-2.0 g/day) in 11.2%. Microscopic hematuria occured in 4.2%. Only 2 patients are hypertensive. Transient serologic abnormalities were seen in 36 patients: elevated IgG in 27, cryoglobulins in 17 and low C3 in 1 patient. Cryoglobulins were found in 50% of the patients with abnormal renal findings and in 22.9% of the patients with normal renal function and urine sediment. Children had urinary abnormalities less frequently (15.1%) than did adults (44.5%). Of 9 patients found abnormal five years ago, 3 were improved or normal, 3 were stable and 3 showed progressive disease.

Our studies indicate that uremia is rare in the first decade after EPSGN; nevertheless the increasing incidence of depressed renal function dictates the need for continued follow-up of this group of patients.

PRELIMINARY ANALYSIS OF THE NATIONAL ESRD MIS DATA 1977-78: PRIMARY ETIOLOGY

SJ Rosansky, T. Sugimoto,* VA Hospital and Dept. of Prev. Med., School of Medicine USC, Columbia, SC

The purpose of this study is to evaluate national end-stage renal disease (ESRD) medical information system (MIS) data in order to formulate epidemiological hypotheses concerning ESRD patients.

The demographic characteristics and percentage distribution of primary diseases leading to ESRD were computed for 21,143 reported patients: glomerulonephritis 29.4, primary hypertensive disease 16.7, interstitial nephritis 11.6, diabetic nephropathy 11.0, unknown etiology 10.4, polycystic kidney disease 9.1, other 7.8, collagen vascular disease (CVD) 1.6, obstructive uropathy 1.56.

Compared to the white population blacks had 3.5 times as much hypertensive renal disease and 1.4 times the frequency of diabetic nephropathy. Compared to the black population whites had 4.4 times the frequency of polycystic renal disease and 2.7 times the frequency of interstitial renal disease. Polycystic kidney disease and interstitial renal disease was 1.6 times as frequent and glomerulonephritis 1.3 times as frequent in females as in males. CVD were 7 times as frequent in black females and 3 times as frequent in white females versus their respective male populations. Males have 3 times as much obstructive uropathy as females.

Confirmation of these data and formulation of appropriate epidemiological hypotheses will be performed utilizing more sophisticated statistical methodology.

PRELIMINARY ANALYSIS OF THE NATIONAL ESRD MIS DATA 1977-78: CAUSES OF MORTALITY

SJ Rosansky, T. Sugimoto,* VA Hospital and Dept. of Prev. Med., School of Medicine USC, Columbia, SC

The purpose of this study is to evaluate national end-stage renal disease (ESRD) medical information system (MIS) data in order to formulate epidemiological hypotheses concerning ESRD patients.

The causes of death by treatment modality and demographic characteristics were analyzed. Selected causes of mortality were compared to the equivalent period prevalence rate in the U.S. general population.

The commonest causes of death in 1134 reported patients were diseases of the heart 36%, cerebral vascular disease (CVD) 10% which is 1.2 times as frequent as the general U.S. population, infection 11.3%, withdrawal from dialysis 6.6%, malignancy 3.5% which was 1/5 as frequent as in the general U.S. population.

Comparing hemodialysis to peritoneal dialysis patients pulmonary infection was 6 times as frequent and withdrawal from dialysis was 2.2 times as frequent. Hyperkalemia and malignancy were 3 times as frequent and GI hemorrhage twice as frequent.

Compared to the total ESRD population white males had 1.4 times the frequency of acute myocardial infarctions, black females had 1.2 times the frequency of CVD and withdrawal from dialysis was 1.3 times as frequent in white females.

Once these results are confirmed with a larger sample size from current ESRD MIS data appropriate hypotheses will be formulated to explain the results.

FABRY'S DISEASE AND RENAL FAILURE: Donald A. Roth, Kumudchandra J. Sheth, and Walter F. Piering, Departments of Medicine and Pediatrics, Medical College of Wisconsin and VA Medical Center, Milwaukee, Wisconsin.

Six male patients from different families were observed with Fabry's disease. Four of these progressed to renal failure requiring dialysis and have had renal transplants with good renal function for 6 months to 8 years (average 42 months). Two of these patients were unusual in that the renal failure occurred at the early ages of 16 and 24 years. One had a transplant with a cadaver kidney, the other from a living related donor and both are doing well. In all cases signs of Fabry's disease were not recognized when the patient first presented to a physician. All 6 had significant proteinuria with an average of 1.2 grams per day. Two patients did not have the typical skin rash, but all were later found to have glycolipid in the urinary sediment, skin or kidney tissue by light and electron microscopy. Diagnosis was confirmed by low serum α-galactosidase level which was less than 0.3 n mole/hr./ml., (normal 11.4±3.5). Early recognition and genetic counseling are important in this disorder in which the diagnosis is often not suspected. The number of female carriers, 3.5 per kindred identified in this small series, suggests that Fabry's disease may become a significant cause of end-stage renal disease. Based on the experience with 4 patients, dialysis and kidney transplantation are appropriate treatment.

RENAL FUNCTIONAL IMPAIRMENT IN DYSAUTONOMIA. R.G. Schacht and D.S. Baldwin. New York Univ. Sch. of Med., Depts. of Ped. and Med., N.Y.

Familial dysautonomia (FD) is an autosomal recessive disorder characterized by widespread autonomic and sensory denervation, postural hypotension and vomiting crises. We have noted elevations of BUN and creatinine uniformly during mild dehydration and often during periods of relative health in the majority FD pts. To determine whether renal functional impairment in FD reflects chronic volume depletion, a renal hemodynamic denervation phenomenon, or parenchymal damage, we measured plasma renin activity (PRA) and renal hemodynamics in 10 ambulatory pts, ages 7 to 32 yrs.

Depressed PRA, 51-200 pg/ml/hr, was observed in all. GFR (inulin) was below the normal of 136 ± 12 in all, ranging from 107 to 43 ml/min/1.73m^2. RPF (p-aminohippurate) was below normal (660 ± 75) in 9 of 10 pts, ranging from 560 to 240 ml/min/1.73m^2. Mean FF was 20.6%. The severity of functional impairment correlated with age.

The proportional reductions in GFR and RPF (normal FF) and the low levels of PRA do not support the thesis that renal vasoconstriction resulting from volume depletion or a hyperreactive dysautonomic renal vascular bed is responsible for decreased renal function in FD.

Renal arteriolar and glomerular sclerosis have recently been described in a group of FD pts with renal functional impairment. We suggest that repeated episodes of hypotension per se and/or renal vascular hyperreactivity to endogenous catecholamine secretion during hypotension may result in such arteriolar and glomerular sclerosis. Autonomic dysfunction is a mechanism which could be responsible for renal parenchymal damage.

● β_2-MICROGLOBULIN (β_2-m) EXCRETION AND IMMUNOFLUORESCENCE OF ANTIBODY COATED BACTERIA (A.C.B.) IN UPPER AND LOWER URINARY TRACT INFECTIONS (U.T.I.). Schardijn, G.H.C., L.W.Statius van Eps, J.P.Persijn*, S.Kok*, A.A.M.Stout-Zonneveld* Depts.of Internal Medicine and Microbiology, Slotervaart Hospital and Depart. of Clinical Chemistry, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.

Urinary β_2-m excretion appears to be a sensitive and specific parameter for tubular dysfunction. As the current method to distinguish between upper and lower U.T.I. with immunofluorescence of A.C.B. is not reliable enough, we investigated β_2-m excretion and compared the 2 methods. 24 hr β_2-m excretion and immunofluorescence studies were performed in 15 patients with upper, 20 patients with lower U.T.I. and 43 control subjects. In patients with pyelonephritis the β_2-m excretion was significantly elevated (range 400-34400 µg/24 hr). Patients with a cystitis had normal values (max.320 µg/24 hr). There was no overlap between the groups. It appears that the use of the β_2-m/creat.ratio is as reliable as the 24 hr excretion to distinguish between these diseases. Due to false negative results of A.C.B. in 27% in upper and false positive results in 25% of lower U.T.I. it is concluded that β_2-m estimation is more reliable. Serial determination of β_2-m appears to be a useful method to control the adequacy of therapy and to detect recurrences; except when other causes of tubular damage are present.

POTASSIUM CHLORIDE THERAPY IMPAIRS URINARY DILUTING ABILITY IN BARTTER'S SYNDROME: A REINTERPRETATION OF THE CHLORIDE LEAK HYPOTHESIS. M. Schambelan, A. Sebastian, and D. Pearce*. Dept. of Medicine, San Francisco General Hospital Medical Center, University of California, San Francisco, CA.

It has been suggested that a defect in chloride (Cl) reabsorption in the loop of Henle is the proximal cause of Bartter's Syndrome based on the finding of impaired urinary diluting ability (Gill et al, AJM 65: 766, 1978). In these studies solute load was supernormal due to KCl treatment for hypokalemia. Because normal urinary dilution is diminished by solute loading, we compared urinary diluting ability before and during chronic KCl therapy (192 mEq/d) in a 31 y.o. man with classic Bartter's syndrome studied twice under identical conditions of water loading and hypotonic saline expansion. Distal chloride delivery ($C_{H_2O}+C_{Cl}$/GFR) and P_{osm} were not significantly altered by KCl therapy (267±1 vs 264±1 mOsm/kg; 13.8±0.8 vs 13.5±0.5%; KCl therapy vs control). However, KCl treatment resulted in significantly greater values of Uosm (92±1 vs 75±1 mOsm/kg; $p<0.001$) and C_{Cl}/GFR (3.8±0.3 vs 2.3±0.3%, $p<0.005$) and significantly lower values of C_{H_2O}/GFR (10.0±0.4 to 11.2±0.3%, $p<0.025$). Fractional distal Cl reabsorption ($C_{H_2O}/C_{H_2O}+C_{Cl}$) was significantly reduced by KCl therapy 0.73±0.01 vs 0.84±0.01, $p<0.001$).

Thus chronic KCl administration significantly diminishes urinary diluting ability in a patient with Bartter's Syndrome. These findings require reconsideration of the hypothesis of a primary defect in Cl reabsorption in patients treated with KCl. Whether the effect of KCl is attributable to suppression of tubular Cl reabsorption or limitation of ADH suppressibility requires further study.

CEFOXITIN INDUCED PSEUDO ACUTE RENAL FAILURE. R.A. Sherman, R.P. Eisinger, M.P. Weinstein* and J. Samel*. CMDNJ-Rutgers Medical School, Depts. of Med. & Path. Piscataway, NJ.

Few substances reach levels in the blood sufficient to interfere significantly with creatinine (Creat) measurement. Cefoxitin (Cef) has been reported to do so and may have led to a misdiagnosis of ATN.

A 65 y/o female with mild stable renal insufficiency was hospitalized with pulmonary edema. Ventricular arrhythmias and hypotension resulted in anoxic encephalopathy. Septicemia with shock developed (11th day) and dopamine, gentamicin, ampicillin and clindamycin were given. Oliguria was noted after a satisfactory BP was achieved (12th day) and resolved on day 13. Cef, 12 Gm/day replaced the other antibiotics on day 13. Lab studies (ASTRA Method):

Hosp. Day:	1	12	14	15	17	18	18
BUN:	27	24	27	26	23	22	23
Creat:	2.2	2.0	3.3	4.1	4.3	3.8	4.6

Cefoxitin was diluted in control sera and "creatinine" levels determined using 3 popular automated systems:

Cef Conc.(µg/ml):	0	50	100	200	600	800
Creat ASTRA	2.1	2.3	2.6	3.1	4.5	5.2
Creat ACA	2.0	2.4	2.6	3.2	5.2	6.2
Creat SMA	2.0	2.1	2.2	2.3	2.8	3.2

In view of the absence of a rise in BUN, the very high dose of cefoxitin, the effect of renal insufficiency on drug accumulation, and the demonstrated effect of the drug on the method used to measure creatinine, pseudo ATN may have been the appropriate diagnosis.

Care is required in interpretation of serum creatinine levels in patients receiving cefoxitin.

LACTIC DEHYDROGENASE (LDH) IS CONSISTENTLY ELEVATED IN THE ADULT NEPHROTIC SYNDROME: FURTHER SUGGESTION OF DISORDERED LIVER METABOLISM IN NEPHROTICS. Martin T. Starkman, Robert M. Centor,* Gregory Miller,* Medical College of Virginia, Richmond, VA.

Serum lactic dehydrogenase (LDH) is an enzyme that is widely distributed in mammalian tissues. It has been appreciated that patients with chronic renal disease may have mild elevations in LDH. This elevation has been attributed to a variety of mechanisms such as renal parenchymal injury, hemolysis and hepatic congestion.

We have observed that there is a strikingly consistent elevation in serum LDH in adult patients with nephrotic syndrome (N.S.) as distinguished from patients with other types of renal disease. This elevation is observed in N.S., regardless of etiology of N.S. or G.F.R.

Fifteen nephrotic patients (mean creat. 2.2) were compared with 18 patients with other types of renal disease (mean creat. 2.8). For inclusion, patients had to have normal SGOT, SGPT, and bilirubin at all times. No patient had evidence of heart failure. The mean LDH was elevated in 14 of 15 nephrotics (93%). In contrast only 4 of 18 (22%) non-nephrotic patients with chronic renal disease had elevated LDH. Patients who had an albumin of less than 3 had a markedly greater incidence of elevated LDH than patients with albumin greater than 3 (P=.0001). There was no correlation between creatinine and LDH. Furthermore, LDH isoenzyme patterns and urinary LDH determinations suggest that the elevation is hepatic in origin.

Conclusions: 1) Serum LDH is routinely elevated in the adult N.S. as opposed to other types of renal disease. 2) The LDH elevation appears to be hepatic in origin.

A MECHANISM OF LOWERED RENIN-ANGIOTENSIN-ALDOSTERONE (R-A-A) SYSTEM IN DIABETIC NEPHROPATHY(DN) K.Tomita*, T.Shiigai*, T.Ideura*, O.Matsuda*, H.Saito*, Y.Iino, Y.Chida*, S.Shinohara*and J.Takeuchi* Dep. of Int. Med., Tokyo Med. and Dent. Univ., Tokyo.

Mechanism of lowered R-A-A system was investigated in 17 patients with DN and 10 control subjects. All subjects were hospitalized and the fasting blood sugar level was controled below 120 mg/100ml. Subjects were grouped according to the basal plasma renin activity (PRA); group I (<0.5 ng/ml/hr), and group II (>0.5ng/ml/hr). Increments of PRA to upright posture were lower ($P<0.01$) in group I (0.62±0.36, m±SD. ng/ml/hr) than group II (1.57±0.68ng/ml/hr) and control group (1.38±0.71 ng/ml/hr). Difference was not observed among all groups in PRA responses to theophylline (500mg drip infusion), which mimics the effect of β-adrenergic stimulation at the receptor sites. Percentage of luminal area of afferent arteriole in biopsy specimen was larger in group I (19.2±2.2%) and control group (21.7±4.3%) than group II (12.4±3.7%). The hyaline change was most significant in group II.

Plasma aldosterone concentration (PAC) was increased by ACTH in all groups, while by angiotensin II PAC increased in group II ($P<0.005$) and control group ($P<0.05$) but not group I (n.s.).

Mechanism of low PRA in DN may not be due to hyaline destruction of the afferent arterioles, but to the sympathetic nerve dysfunction. In this group, adrenal responses of PAC to angiotensin II may also be impaired.

LESSONS FROM ONE HUNDRED ARTERIOGRAPHICALLY CONTROLLED PERCUTANEOUS RENAL BIOPSIES (ACPRB). Charles Swartz and Audrey Wilson*, Depts. of Med. and Rad., Hahnemann Medical College and Hospital, Phila., Pa.

In order to determine if it is possible to eliminate hemorrhage or formation of arteriovenous fistula after percutaneous renal biopsy, 100 patients underwent ACPRB. Thirty-eight patients were in a group who would have undergone surgical biopsy because of azotemia or accelerated hypertension. Sixty-two patients were in a clinical group who would have undergone renal biopsy under pyelographic or sonographic localization. There were ten significant post-biopsy hemorrhages defined as a requirement for transfusion or a decrease in Hgb of 2 gm%. They were equally divided between the high and normal risk group. All hemorrhages were immediately obvious with massive extravesation of contrast media. In three of five patients, epinephrine vasoconstriction abruptly stopped the bleeding. All eight hemorrhages involved biopsy cuts more than 2 cm from the kidney edge. The bleeding was invariably a result of a vessel severed by the cutting cannula. On occasion, the cephelad angle of the cutting needle resulted in a cut more than 2 cm from the kidney edge despite placement of the needle tip within the safe zone.

We have learned from ACPRB that there is a narrow safe zone of biopsy. All biopsy cuts are now made from the center toward periphery of the kidney. ACPRB provides immediate reliable indication of post-biopsy bleeding. Epinephrine vasoconstriction is useful to limit hemorrhage in some cases.

CLINICAL CHARACTERISTICS OF PATIENTS WITH THE SYNDROME OF HYPORENINEMIC HYPOALDOSTERONISM (SHH). J. Uribarri*, M.S. Oh, H.J. Carroll. State Univ. of N.Y., DMC, Brooklyn, N.Y.

Studies on SHH have usually concentrated on measurements of renin, aldosterone and electrolytes in small numbers of patients. The present study describes certain other important clinical characteristics in a large series of patients. Evaluation of sustained hyperkalemia during an 18-month period identified 30 patients with SHH: plasma renin activity (PRA) and plasma aldosterone (PA) below normal in the presence of hyperkalemia.

The patients age was 57 ± 1.7 (SD) years; these were 15 men and 15 women. Serum K was 5.9 meq/l ± 0.37. PRA before stimulation was 1.24 ng/ml/hr ± 0.6, and after furosemide 1.53 ± 0.63. Our control PRA after furosemide is 4.2 ± 2.7. PA was 3.1 ng/dl ± 1.7 before, and 6.1 ± 2.9 after stimulation. Control PA after furosemide is 20.2 ± 8.4. 20 patients had high blood pressure, 11 congestive heart failure, 9 hyponatremia and 19 metabolic acidosis. All patients had renal disease; Serum creatinine was 2.9 mg/dl ± 1.7. 14 patients had diabetic nephropathy, 7 chronic tubulointerstitial disease and 9 various other diseases. Urinary K:Na ratio was 0.42 ± 0.16; for patients with hyperkalemia due to dehydration (high aldosterone and no tubular secretory defect) the ratio was 8.7 ± 2.9.

In our experience SHH is the commonest cause of sustained hyperkalemia and it is most often associated with diabetes or chronic interstitial renal disease. The frequent occurence of hypertension despite low PRA and PA suggests volume expansion as a likely cause of renin suppression and secondary hypoaldosteronism.

METABOLIC ACIDOSIS ASSOCIATED WITH PAINT SNIFFING. Anne Voigts,* Christian E. Kaufman, Jr., Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

Metabolic acidosis due to the inhalation of spray paint is described in 8 patients observed during 16 hospitalizations. All presented with nausea, vomiting, abdominal pain and acidosis (arterial blood pH (6.88-7.38). Pyuria (6/16), hematuria (11/16), and proteinuria (12/16) occurred frequently suggesting diffuse nephron injury. During 12 episodes of acidosis the "anion gap" was normal. In 7 of these cases a urine pH >5.5 indicated renal tubular acidosis (RTA). In 5 cases urine pH <5.5 suggested proximal RTA or rapid recovery of renal acidifying ability. One patient during 2 hospitalizations demonstrated hypocalcemia (7.5-7.7 mg%), hypouricemia (1.8, 1.5mg%) and hypophosphatemia (1.2, 1.8mg%) suggesting proximal tubular dysfunction. Isolated hypophosphatemia (0.6-2.8mg%) was observed during 7 episodes, and hypokalemia (1.9-3.2 mEq/L) on 8 occasions. Azotemia (serum creatinine 1.7-5.4 mg%) was noted during six episodes and in 4 cases was associated with a high "anion gap". In 2 patients urinary acidification was assessed before and after bicarbonate therapy. Baseline excretion of titratable acid was normal in both, while ammonium excretion was elevated (131 μEq/min, 595 μEq/min), perhaps related to potassium depletion or rapid recovery of tubular function. Bicarbonate excretion remained low ($FeHCO_3$ 0, 1.5%) despite significant increments in plasma bicarbonate concentration. We conclude that paint inhalation may cause severe metabolic acidosis often accompanied by hypokalemia, hypophosphatemia or renal failure. Transient distal RTA occurs but does not explain many of the features of this syndrome.

ANALYSIS OF END-STAGE RENAL DISEASE (ESRD) PATIENT SURVIVAL DATA. John M. Weller, Friedrich K. Port, Richard D. Swartz, C. William Ferguson*, George W. Williams*, and John F. Jacobs, Jr. Nephrology Division, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

The life-table analysis of ESRD patient survival ignores the fact that patients experience sequential risks as they undergo successive treatment modalities such as dialysis and transplantation. Two new types of analysis which address this are: 1) a sequential graphic method and 2) a transient state modification of the life-table analysis. The sequential method visually presents the survival experience of ESRD patients during successive treatments. The transient state method takes into account the time to treatment bias, e.g., the experience with initial center dialysis, and incorporates subsequent accession to home dialysis or transplantation. Analysis of 2,493 ESRD patients in Michigan from 1974-1978 by the life-table method shows one and two year survival percentages, respectively, for home dialysis, related transplant and cadaver transplant patients of 86.1 and 75.3, 91.0 and 89.4, and 75.2 and 69.1. Corresponding values for the sequential method are 76.9 and 67.2, 78.1 and 76.8 and 58.0 and 53.3. The transient state method shows significantly better survival for both home dialysis and related transplant patients compared to center dialysis patients ($p < 0.001$ for each), but no difference between cadaver transplant and center dialysis patients ($p = 0.33$). These two modifications of the life-table analysis method present a more realistic view of the survival experience of ESRD patients treated by successive modalities of therapy.

GLOMERULAR DYSMEMBRANOSIS: AN UNUSUAL CAUSE OF CHRONIC GROSS HEMATURIA. K. Wallner*, L. A. Hebert, W. H. Bay, H. M. Sharma and R. H. Smith* Depts. of Med. and Path., The Ohio State Univ., Cols., Ohio

Renal biopsy is generally not thought to be of value in the diagnostic evaluation of the patient with chronic gross hematuria (GH) because glomerulopathies have seldom been identified as causing chronic GH. We present a patient in whom the renal biopsy did provide the solution to a perplexing problem of chronic GH. The patient, a 20-year old black male, first noted GH and bilateral flank pain after completing an intercollegiate basketball game in Oct. 1979. Physical exam was normal except for bilateral flank tenderness. Urinalysis showed 1+ protein in a grossly bloody sample. Urine sediment showed innumerable red cells. Serum creatinine was 1.2 mg/dl. IVP was normal. Cystoscopy showed blood issuing from both ureters. Comprehensive testing, including coagulation and sickle cell studies, showed no abnormalities. However, certain in vitro tests of platelet function were abnormal. Renal biopsy showed normal glomeruli by light and immunofluorescent microscopy but in many areas the tubules were widely dilated and some were filled with blood indicating a glomerular site of bleeding. Electron microscopy showed marked focal thinning of GBM with dark, circular inclusions. Alport's syndrome was suspected but urinalyses on parents and siblings were normal. HLA typing showed that his putative parents are his biological parents. GH is constant, and increases with exercise which causes flank pain. GH has not been controlled with bed rest or platelet transfusion. We conclude that glomerulopathy can cause chronic GH. Renal biopsy should be considered in patients with chronic GH particularly those with bilateral hematuria.

ULTRASONIC DETECTION OF COMPLICATIONS FOLLOWING RENAL BIOPSY. RL Winer, SJ Handler* (Intr. by G Shah) Depts. of Medicine/Radiology, VA Med Cntr., Long Beach, and University of California, Irvine.

A known complication of percutaneous renal biopsy is perirenal hematoma formation, the incidence of which has been suggested to be very low (1.4%). In this study, 27 male patients (25-72 y/o) with a variety of renal parenchymal disorders (S_{cr} 0.9 - 8.2 mg/dL) had a diagnostic percutaneous renal biopsy. Conventional gray-scale ultrasound was used to localize the position and depth of the kidney's inferior pole for the biopsy and to monitor the development and course of hematomas. There was no history of bleeding diathesis, and PT, PTT, and platelet counts were normal. 25 of 27 patients had ultrasonically detectable perirenal and occasional intrarenal hematomas within 24 hours of the biopsy and there was complete hematoma resolution in 1 to 8 months. Only 1 patient had clinical manifestations (mild hypotension and fall in hematocrit) from a large intrarenal hematoma. There was insufficient tissue for diagnosis in 3 patients (11%); however, 2 of these developed small perirenal hematomas. In a computerized tomography study (KI 14:87,1978) the incidence of post biopsy hematomas was 85%. This is supported by our data in that 93% of patients had ultrasonic evidence of hematoma formation. The previously reported low incidence of hematomas may, in part, be explained by reliance on hematocrit and blood pressure changes. We have demonstrated that ultrasound is an effective and safe imaging modality for percutaneous renal biopsies, and is a sensitive tool for detecting hematoma formation and resolution. The incidence of post-biopsy hematomas is quite high, although clinically silent.

PHARMACOKINETICS OF AMANTADINE HYDROCHLORIDE IN PATIENTS WITH IMPAIRED RENAL FUNCTION (IRF). M.J. Wu, T.S. Ing, L.S. Soung*, J.T. Daugirdas*, J.E. Hano and V.C. Gandhi. Veterans Administration Hospital, Hines; Loyola University Stritch School of Medicine, Maywood; Illinois.

To study the disposition of amantadine hydrochloride in patients with impaired renal function, 100 mg. was administered orally to 13 patients with creatinine clearances of 10 to 53 ml./min. Six healthy individuals served as controls. In both groups, stool recovery during the first 72 hours was less than 1.0 mg., suggesting good absorption. In IRF patients, a peak plasma level of 348 ± 30 (SEM) ng./ml. (373 ± 31 in controls) was reached 3.1 ± 0.4 hours after ingestion (1.7 ± 0.2 hours in controls). The apparent volume of distribution was large, 4.5 ± 0.3 L./Kg. of body weight (4.8 ± 0.4 in controls), suggesting substantial tissue binding. Renal amantadine clearance was lower in IRF patients (range 21.4 to 180.6 ml./min., mean 55.1 ± 13.9) than in controls (mean 248.1 ± 40.9). Renal amantadine clearance substantially exceeded creatinine clearance in both IRF patients and controls, suggesting that amantadine is secreted by the renal tubules. Plasma half-life was prolonged in IRF patients (range: 26.9 to 144.4 hours, mean 68.5 ± 9.5) relative to controls (mean 12.6 ± 1.7). Plasma half-life was significantly correlated with serum creatinine levels ($r = 0.85$, $p < 0.001$).

Our results suggest that: (1) amantadine has a large apparent volume of distribution, (2) it is secreted by the renal tubules, and (3) its elimination in IRF patients is delayed. The dose of amantadine should be reduced when treating patients with renal insufficiency.

● PULMONARY FUNCTION TESTING DURING PERITONEAL DIALYSIS. Ahluwalia MPS,* Sekar T,* Moorthi DS,* Gelman ML, Shah T,* Doherty GB,* MacDonnell KF.* St. Elizabeth's Hosp. of Boston, MA.

Alteration in pulmonary function tests produced by the addition of 2L of dialysate to the peritoneal cavity were examined in six patients with chronic renal failure (5 females, 1 male) ages 39-78. No difference was found in the vital capacity (VC), forced expiratory volume in one sec. (FEV_1) or closing volume (CV/VC) during any phase of the study. Functional residual capacity (FRC)was significantly reduced*($P<0.01$) with 2L dialysate in the peritoneal cavity. All the subjects showed a decrease in residual volume (RV), but this was not statistically significant. The decrease in FRC appeared to be mostly due to a decrease in RV, the ERV remaining unchanged. The mean weight loss at the end of dialysis was 1.7 Kg and the change was significant ($P<0.002$).(ERV=expiratory residual volume).

	VC L Mean ±SD	FEV_1 L Mean ±SD	CV/VC % Mean ±SD	FRC L Mean ±SD	RV L Mean ±SD	ERV L Mean ±SD
Before PD	2.1± 0.45	1.6± 0.34	14±5	2.1± 0.39	1.4± 0.33	0.67± 0.22
With 2L dialysate	2.1± 0.44	1.6± 0.38	15±3	1.8±* 0.28	1.2± 0.30	0.63± 0.26
After 8 hrs. PD	2.1± 0.47	1.5± 0.36	11±5	2.1± 0.08	1.5± 0.38	0.66± 0.16

(PD=peritoneal dialysate).

Our findings do not support previous data of a decrease of VC with 2L dialysate.

Dialysis

● HYPOXEMIA DURING BICARBONATE DIALYSIS. D.K. Abu-Hamdan*, S.K. Mahajan, S. Desai*, C.W. Choi*, B. Mueller*, W.A. Briggs, and F.D. McDonald, V.A. Medical Center, Allen Park, Wayne State Univ. Detroit, MI

Significant hypoxemia invariably occurs during acetate dialysis. Recent reports indicate that bicarbonate dialysis prevents dialysis-related hypoxemia. We studied 7 patients before and during dialysis with arterial blood gases, respiratory quotient (R) and alveolar-arterial oxygen gradient ($A\text{-}aO_2$). Each patient was dialyzed against either an acetate or a HCO_3 bath. Exactly one week later, each patient was dialyzed against the opposite bath.

Mean ± SEM, †$P < 0.05$ from base line.

Arterial PO_2 (PaO_2) mmHg

	0'	15'	30'	60'	120'	180'
Bicarb.	87.3 ± 2.7	†80.6 ± 3.7	† 75.4 ± 4.5	†75.7 ± 2.8	77.8 ± 4.5	†76.3 ± 4.1
Acetate	89.6 ± 5.2	†80.3 ± 3.1	†74.4 ± 4	†78.7 ± 3.9	76.2 ± 5.9	80.8 ± 3.3

A significant drop in mean PaO_2 occurred within 15 minutes and persisted during both acetate and bicarbonate dialysis. There was no significant difference between PaO_2 on bicarbonate dialysis vs. acetate dialysis. R decreased during acetate dialysis ($P < 0.01$) but not during bicarbonate dialysis. The preservation of R in those dialyzed against bicarbonate, in the face of hypoxemia similar to that of patients dialyzed against acetate, suggests that: (1) a change in R is not the sole mechanism for hypoxemia during hemodialysis and (2) a mechanism common to patients dialyzed against either bath is likely.

THE ROLE OF HYPOXEMIA IN THE EXPRESSION OF ACETATE INTOLERANCE. S. Ahmad,* M. Pagel,* F. Shen,* J. Vizzo,* and B. H. Scribner. Dept. of Medicine, University of Washington, Seattle, WA.

Symptoms of acetate intolerance are strikingly similar to those of hypoxemia. In 20 dialysis patients significant hypoxemia was noted during acetate dialysis. Hypoxemia was later prevented in 4 acetate intolerant patients with nasal administration of 2 L/min of O_2. Since acetate related symptoms also were markedly reduced in these 4 patients a larger prospective randomized blind study comparing administration of 2 L/min of air (AA) with 2 L/min of O_2 (AO) during acetate (38 mEq/L) dialysis was initiated. Five acetate intolerant and 5 acetate tolerant patients each were dialyzed 4 times on AO and 4 times on AA. Tolerant patients showed no difference between air and O_2 trials in acetate related symptoms, mean BP drops, and objective reaction time test performance. However, intolerant patients had significantly less mean BP drop on AO than on AA ($\bar{x}$ = 11.8 vs 17.8, $p < 0.04$), 14 AO vs 27 AA incidences of nausea, vomiting and/or headache ($p < 0.02$), and significantly less pre- to postdialysis slowing of reaction time (11.7 msec AO vs 33.0 msec AA, $p<0.02$). Thus, correction of dialysis hypoxemia greatly reduced acetate intolerance and improved the quality of dialysis. Tolerant and intolerant patients did not differ in age, body weight, body surface area, hct, or presence of LVH. However, only among intolerant patients did the hct correlate significantly with symptoms and mean BP drop ($r = -0.85$, $p < 0.04$), but not with reaction time. In conclusion, the use of oxygen allows intolerant patients to dialyze against acetate without discomfort.

A STUDY OF INFLAMMATORY PARAMETERS ON EARLY ASYMPTOMATIC PERITONITIS IN CHRONIC PERITONEAL DIALYSIS PATIENTS. *N. Alavi,* E. Lianos,* B. Mookerjee and T. Beam*. Dept. of Medicine, SUNY at Buffalo, N.Y.*

In order to investigate changes in inflammatory parameters in asymptomatic peritonitis and their alteration by antibiotic therapy (Rx), 8 patients (pts) undergoing intermittent chronic peritoneal dialysis were selected on the basis of positive peritoneal fluid cultures. The predominant pathogen was staphylococcus aureus. Each pt was studied prior to initiating therapy (pre-Rx) and 3 wks following antibiotic therapy when cultures were negative (post-Rx). Comparisons were made with 9 uninfected pts on peritoneal dialysis (control). Peritoneal fluid obtained 12 to 16 hrs after the last dialysis were analyzed for:

Parameter	*Control*	*Pre-Rx*	*Post-Rx*
Lactate	*9.7±2*	*21±2**	*12.8±2*
WBC	*300±86*	*6000±1500**	*861±187**
LDH_5	*7.6±1.5*	*23.8±4**	*7.0±1.9**
IgA	*55±9*	*88±16**	*98±2*
IgM	*7.2±3*	*17±4**	*18±8*

** p<.05*

No changes in the above parameters were found in blood samples. Peritoneal fluid pH was 7.58±0.03 both in control and infected pts. Although all LDH fractions were increased during infection the increments were significant only for fraction 5. We conclude: (a) Changes in parameters investigated reflect local inflammatory phenomena only; (b) Evaluation of the above parameters, mainly lactate, WBC and LDH are helpful in early detection of peritonitis in patients undergoing peritoneal dialysis.

SEVERE HYPERGLYCEMIA IN DIABETIC DIALYSIS PATIENTS. R.R. Al-Kudsi*, J.T. Daugirdas*, T.S. Ing, A.O. Kheirbek*, W.T. Chen, J.E. Hano, and V.C. Gandhi. Veterans Administration Hospital, Hines; and Loyola University Stritch School of Medicine, Maywood; Illinois.

In 11 insulin-dependent diabetic patients who were being treated with maintenance dialysis, extremely high glucose levels were observed for short time intervals without apparent neurologic deficit. Four patients were on hemodialysis, 6 on peritoneal dialysis, and 2 on continuous ambulatory peritoneal dialysis. Mean duration of dialysis was 5.2 ± 1.8 (SEM) months. Mean age was 54.2 ± 2.2 years. Hyperglycemia was believed to be related to use of glucose-containing dialysates, to use of steroids, and/or to infection.

Mean serum values: calculated total osmolality 340.3 ± 4.0 mOsm./Kg. water, calculated effective osmolality (without urea) 314 ± 3.6 mOsm./Kg. water, glucose 1,146 ± 72.6 mg./dL., sodium 125.3 ± 1.6 mEq./L., urea nitrogen 74.4 ± 7.0 mg./dL., potassium 4.7 ± 0.2 mEq./L., bicarbonate 19.9 ± 0.9 mEq./L. The patients' mean weight was 2.4 ± 0.7 Kg. above their regular "dry" weight.

All patients remained alert, well oriented, and neurologically stable. The extreme hyperglycemia was corrected within 24-48 hours with small additional doses of regular insulin. Our results suggest that the lack of osmotic diuresis, and the use of only modestly hypertonic dialysate in the peritoneal dialysis patients (dextrose less than 4.5%) prevented the development of hypernatremia and marked hyperosmolality. The osmolar effect of glucose alone at these serum levels apparently was not sufficient to induce neurologic impairment or coma.

● DISCORDANCE BETWEEN SERUM FERRITIN AND BONE MARROW IRON IN DIALYSIS SIDEROSIS. M. Ali*, R. Rigolosi, J. Frascino, R. Singer, and A.O. Fayemi*. Regional Hemodialysis Center, Teaneck, New Jersey.

Semiquantitative scores for stainable iron in the bone marrow and hepatosplenic compartments of the reticuloendothelial system were correlated with serum ferritin levels in 36 hemodialysis patients at autopsy. Two or more Prussian blue stains of each organ prepared with appropriate controls were scored for iron on a scale of 0-4+. There were 23 males and 13 females with a mean age of 61 years. All patients were anemic (Hb<10 gm/dl). The mean duration of dialysis for 29 patients treated for more than six months was 39 months; the mean values for elemental iron given intravenously as iron-dextran and units of blood or packed cells in this group were 5450 mg, and 9.8 units respectively.

The serum ferritin levels ranged from 28 to 4950 ng/dl and correlated well with the hepatosplenic iron scores; as the iron deposits in the tissue increased so did the values for serum ferritin (r, 609; P<.001). As for the correlation with bone marrow, low ferritin levels were associated with diminished or absent marrow iron. However, high serum ferritin levels in presence of hepatosplenic siderosis did not always correlate with the marrow iron (r,.42; P<.01). Thus, the ferritin levels were raised in ten marrow-iron-depleted patients (mean, 1336 ng/dl). The association of hepatosplenic siderosis with marrow-iron-depletion, and the resulting disagreement between serum ferritin and marrow iron, may be explained on the basis of selective uptake and release of iron bound to transferrin. Thus, the peripheral plasma iron in man seems to be preferentially removed by the liver and spleen as hypothesized in rabbit by Fletcher and Huehns and shown in mice by Okada et al.

● HEMODIALYSIS ACCESS MORBIDITY. Linda C. Aman,* Nathan W. Levin, Henry Ford Hospital, Division of Nephrology, Detroit, Michigan, David W. Smith,* University of Michigan, Statistical Research Laboratory, Ann Arbor, Michigan.

A retrospective analysis of internal access survival was made in 465 patients from 9 dialysis units in S.E. Michigan. Both complication-free (CF) and total survival (T) of accesses were calculated for A-V fistulae (AVF), bovine (B), and PTFE grafts, and analyzed by age, sex, race and diagnosis. 1 yr. T of AVF was significantly better in males (85%) than in females (73%), whites (87%) than in blacks (76%), and non-diabetics (83%) than in diabetics (67%). Surprisingly T for B and PTFE grafts was not influenced by any of these factors since 1 yr. T of B grafts was not different in males and females (75%); whites (70%) and blacks (77%), non-diabetics (75%) and diabetics (76%). T for PTFE grafts was generally lower in each category but with similar trends as for B. CF for AVF in blacks and whites was similar. Neither age nor the presence of hypertension affected CF or T. Thrombosis accounted for 55%, and infection for 17%, of dialysis complications requiring hospitalization. Single needle dialysis with 14G needles was associated with decreased AVF and PTFE graft survival. The incidence of infection appeared to be related to different methods of skin cleansing prior to hemodialysis. Costs of the treatment of access complications averaged $750./patient/year in this group excluding costs of laboratory investigations, antibiotics, and IV solutions. Prorating this ≈1% sample of the U.S. dialysis population suggests that >$40-50,000,000. are spent annually on the treatment of access complications.

MICROPROCESSOR CONTROL OF BLOOD FLOW IN A SINGLE NEEDLE, RECIPROCATING, SORBENT SUSPENSION DIALYZER (SSRD). Stephen R. Ash, Randall H. Roberts,* and Ben Hillberry *, Hemodialysis Laboratory, Purdue University, West Lafayette, IN

The SSRD is a parallel plate dialyzer with a suspension of sorbents in the dialysate space and a single blood entry port. Pressure alterations in the dialysate result in inflow and exit of blood from the membrane packages. While this dialyzer can be operated by a simple pressure-vacuum pump (ASAIO, 1980), this pump is bulky, energy inefficient, insensitive to venous collapse, and occasionally incomplete in filling or empyting of the dialyzer. For these reasons, a microprocessor control system was developed with an 8.K Rom, A-D converter, ultrasonic flow probe, DC motor, expandable bellows, and a dialysate pressure monitor (pressure transducer or motor ammeter). Blood flow into and out of the dialyzer is monitored by the flow probe, and the dialysate pressure reversed after complete emptying or filling. A preset program finds the maximal inflow rate which avoids vein collapse.

Tests of the control system were performed on dogs with A-V shunts or central venous cannulae, utilizing a 30 package SSRD model (0.7 M^2). Inflow and outflow rates were similar to those obtained with the pressure-vacuum system. Inlet obstruction (venous collapse) was successfully recognized, and the flow to the dialyzer successfully optimized. The microprocessor control will aid in the use of the SSRD as a portable,self-contained, single needle dialyzer.

ANALYSIS OF FACTORS CONTRIBUTING TO OVER TEN YEARS LONGEVITY ON LONG-TERM HEMODIALYSIS. M. M. Avram, Abe Pahilan* A. Gan, Paul Slater, Paul Fein, Michael Iancu. The Long Island College Hospital, Div. of Nephrology, Dept. of Med., Brooklyn, N.Y.

To discern factors contributing to long-term survival on maintenance hemodialysis (MH), we analyzed the course of 158 uremic patients who began MH between 1968 and 1970, including 32 (20.2%) who lived for at least 10 years. Of the long survivors (LS) 18 (56.2%) are still on MH. The LS were compared with 50 randomly selected control MH patients and with a group of patients who had completed a decade of MH and then died. Parathyroid hormone level (PTH) was lower (523±379.8pg/ml) in living LS patients than in those who died (672.4±180.1pg/ml) ($p<.05$) or in the controls (931±803pg/ml) ($p<.02$). In both living long-term patients and in controls, the severity of impairment of motor nerve conduction velocity was inversely proportional to the height of PTH. LS had hematocrits inversely related to PTH. Following subtotal parathyroidectomy in 7 living long-term patients, mean hematocrit rose from 15.6±1.9% to 26.4±2.6% and mean PTH levels decreased from 1632.6±408pg/ml to 341.1±106.4pg/mg. The long surviving MH patients were predominantly female (61%) and were younger when starting MH (mean age 31.7 yrs.) than the controls (mean age 41.1 yrs.). Serum phosphate level (4.1±0.7) was lower than in controls (4.9±1.4) ($p<.05$). Binephrectomy had been performed in 7 LS patients. Greater motivation, rehabilitation and better angioaccess were noted in all LS compared with controls. We conclude that some patients after 10 years MH are in remarkably good condition, and we profiled factors contributing to their longevity.

HYPERTENSION TREATMENT WITH CAPTOPRIL IN DIALYSIS PATIENTS. Mattias Aurell*, Henric Mulec* (intr. by Joseph W Eschbach). Department of Nephrology, Sahlgrenska Hospital, Göteborg, Sweden.

Seventeen dialysis patients (15 HD, 2 CAPD) with poor blood pressure (BP) control or side-effects on standard treatment were treated with the angiotensin converting enzyme inhibitor captopril (SQ 13225) 12,5-450 mg/day. HD-patients were dialysed 3 times/week. The short-term BP-lowering effect of 25 mg was tested the day after dialysis for HD-patients and during CAPD, 8-12 a.m. Previous BP-treatment was stopped the day before testing. Reduction of mean BP was obtained up to 40 mm Hg in some patients, and the response correlated with the initial plasma renin activity (PRA) ($r= 0,65$, $p<0,001$). At follow-up of 9 long-term treated patients (mean 5,3 months) maintained on a mean dosage of 162 mg/day (range 12,5-450 mg per day) systolic and diastolic BP decreased from $177 \pm 8/109 \pm 3$ to $149 \pm 3/94 \pm 2$ mm Hg, mean BP from 133 ± 4 to 112 ± 2 mm Hg ($p<0,001$). There was no correlation between the long-term BP-effect and initial PRA, in striking contrast with the short-term effect. Treatment was stopped in only one patient due to lack of effect, which was attributed to poor fluid control. Two patients stopped treatment due to adverse effects (urticaria and nausea). It is concluded that captopril is a potent antihypertensive drug in most dialysis patients, and appears to be a valuable drug in long-term hypertension treatment. Side-effects appeared within the first months of treatment. Patients on long-term treatment may be safely maintained on a dosage of 150-200 mg/day.

● EFFECT OF LONG-TERM DIALYSIS (D) ON LEFT VENTRICULAR EJECTION FRACTION (LVEF) IN END-STAGE RENAL DISEASE (ESRD). J. C. Ayus, P. Frommer*, J. J. Olivero and J. B. Young*. Baylor College of Medicine, Houston, Texas.

Cardiovascular abnormalities are the leading cause of death in patients (pts) with ESRD on D. No prospective studies on the effect of chronic D on cardiac function are available, thus the long-term effect of this treatment remains unsettled. We therefore prospectively evaluated LVEF in 50 pts (25 male, 25 female) with ESRD who were about to initiate D, using M-mode echocardiography. The mean pt age was 49 years (range 18 - 80). Pre-D mean LVEF was 0.56 ± 0.02 (± SE), however, 19 pts (39%) had a depressed LVEF (<0.50).

Thirty-three pts of the original group were re-studied after 9.9 ± 1.7 months of chronic D. The mean pre-D LVEF for this group was 0.51 ± 0.03 which improved significantly to 0.57 ± 0.03 ($P<0.05$). In order to clarify which group benefited the most with D, we further subdivided the follow-up population into those pts who had an abnormal pre-D LVEF (group A) and those with a normal pre-D LVEF (group B). There was normalization of LVEF in group A (0.37 ± 0.02 to 0.50 ± 0.03; $P<0.001$), while group B remained unchanged (0.63 ± 0.03 to 0.62 ± 0.03; P = NS).

Our results show (1) that there is a high prevalence (39%) of left ventricular dysfunction in pts with ESRD prior to the initiation of D, (2) pts with pre-D abnormal LVEF normalized this parameter after chronic D, (3) those pts with a normal pre-D LVEF did not deteriorate during D. Thus, long-term D has a beneficial effect on cardiac function in pts with ESRD, particularly on those who begin D with left ventricular dysfunction.

RECIRCULATION (R) IN SUPERIOR VENA CAVA (SVC) TWO NEEDLE DIALYSIS. David B. Baldwin* and Dale Rowett, Middlesex Hospital, Middletown, Ct.

Because of problems with external arteriovenous shunts and femoral vein dialysis cannulas in acute renal failure, a subclavian dialysis cannula has been used in conjuction with a single needle device. This cannula can also be used in the internal jugular vein. R, using this SVC cannula for blood draw, and an antecubital vein for blood return, was studied. 5 patients with acute renal failure had 18 dialysis treatments, using the Uldall dialysis cannula via the subclavian vein (10 treatments) and the internal jugular vein (8 treatments). A 14 gauge Deseret dialysis cannula in an antecubital vein was used for blood return. R was calculated for urea and creatinine at blood flow rates of 180 and 300 ml/min, using: $R = \frac{Cp - Ca}{Cp - Cv}$

Where Cp is the concentration in a separate peripheral vein, Ca is the concentration in the ingoing dialyzer line, and Cv is the concentration in the outgoing line.

R was remarkably constant, ranging between 12-15% for each dialysis treatment over both flow rates. This R in two needle dialysis is similar to or better than the R for single needle dialysis, and more predictable. It is concluded that R does not prevent the use of the SVC for two needle dialysis.

ENHANCEMENT OF PERITONEAL TRANSPORT WITH IMIDAZOLE (IM), A THROMBOXANE SYNTHETASE INHIBITOR. John D. Bell, Larry W. Thorpe,* R. Robert Hatlelid,* and Robert E. Lynch, Univ. of Texas Med. Br., Galveston, Texas.

Previous studies by others have shown peritoneal solute transport to be either augmented or decreased by intraperitoneal (IP) administration of selected prostaglandins (PG). In order to further investigate PG action on peritoneal transport, the effects of a selective PG pathway inhibitor, IM, was evaluated. Peritoneal dialyses were performed on Sprague-Dawley rats, weighing 250-350 gm., utilizing a commercial dialysate containing 1.5% dextrose. IM was added at a dosage of 10 mg./35 ml. exchange during the experimental period. Two control dialysis exchanges were done in each animal (Period A), followed by two IP drug exchanges (Period B), and terminated by two post-drug exchanges (Period C). Results were as follows:

Period		K urea (ml/min)
A	(Control)	.486 ± .066
B	(Drug)	.569 ± .071
C	(Post-Drug)	.570 ± .043

A significant enhancement of urea transport ($p<.05$) was observed with IP administration of IM compared to control levels. This increase persisted in the two post-drug exchanges compared with control periods ($p<.05$). It is concluded that IM significantly enhances peritoneal urea transport. Further elucidation of solute clearance effects of IM and investigation of its mechanism of action are in progress. Assessment of its potential use in clinical peritoneal dialysis also may be warranted.

CIMETIDINE THERAPY OF TERTIARY HYPERPARATHYROIDISM IN HEMODIALYSIS PATIENTS. W. H. Bay, L. A. Hebert, J. B. Cornacoff* and R. A. Zager, Dept. of Med., Ohio State Univ., Columbus, Oh.

Recent data suggest that cimetidine (CIM) therapy controls the hyperparathyroidism (HPT) accompanying renal failure. We studied three patients (pts) with tertiary HPT defined as hypercalcemia and HPT occurring after several years of secondary HPT. Each pt had immunoreactive parathyroid levels >20,000pg/ml (C terminal assay, normal <2,000pg/ml) on multiple occasions. The pts were studied before, during and after 6-9 wks of oral CIM. Pts A and B received CIM 900mg/day. Pt B received 2 courses of CIM, B1 and B2 respectively. Pt C received CIM 300mg/day because larger doses caused GI distress. There were no changes in dialysis schedules or medications. Pts were observed for 12-24 wks before and for 7-15 wks after CIM. The effect of CIM on serum calcium is shown below:

	SERUM CALCIUM (mg/dl)		
Pt.	Pre-CIM	CIM	Post-CIM
A	12.3±.3,* n=5**	11.2±.1, n=7	11.2±.2, n=6
B1	11.1±.2, n=7	10.4±.2, n=3	11.6±.1, n=4
B2	11.6±.1, n=4	10.8±.4, n=3	parathyroidectomy
C	10.8±.1, n=4	11.0±.1, n=6	10.6±.1, n=7

* mean ± SE, ** number of measurements

There were no significant changes in serum phosphorus, albumin, or alk p-tase levels during the study. After completing the second course of CIM therapy, Pt B had a subtotal parathyroidectomy. Four hyperplastic parathyroid glands were identified. These data show that CIM, in doses >300mg/day, lowers serum calcium levels. We conclude that cimetidine therapy can play a role in the management of the tertiary HPT of chronic hemodialysis patients.

PLACEMENT OF THE TENCKHOFF PERITONEAL CATHETER UNDER DIRECT VISION UTILIZING THE NEEDLESCOPE® Richard Bloch, and Stephen R. Ash, Hemodialysis Laboratory, Purdue Univ., W. Lafayette, IN and Arnett Clinic, Lafayette, IN

The Tenckhoff catheter has been remarkably successful as a long term access device to the peritoneum. However, placement of the Tenckhoff catheter by blind trocar insertion often results in malposition, with resultant outflow obstruction. Surgical placement often makes immediate initiation of dialysis difficult, and sometimes results in leaks around the peritoneal catheter.

A new method of placement of the Tenckhoff catheter has been devised utilizing an initial inspection of the abdomen with the Needlescope®. This 2.2 millimeter diameter rigid endoscope allows inspection of the abdomen before and after air insufflation. A slotted polypropylene tube, rolled in a tight coil, is carried into the abdomen around the Needlescope®. This serves as a guide for the placement of the Tenckhoff catheter, allowing proper placement of the cuff, and minimal leak around the catheter. The catheter may, using this technique, be directed into the free space between abdominal wall and bowel loops.

Tenckhoff peritoneal catheters have been placed in 20 patients over the past two years, utilizing this technique. Only one early catheter failure has been encountered, and long term function of the catheters is satisfactory. The technique allows placement of the Tenckhoff catheter in patients who have had numerous previous abdominal surgeries. A color, sound motion picture has been produced, to thoroughly demonstrate the placement technique.

BICARBONATE (Bi) IS NOT BETTER THAN ACETATE (Ac) IN ACUTE DIALYSIS. H. Borges,* D. Fryd,* C. Kjellstrand. Univ. of Minn., Minneapolis, Minn.

Bi dialysate is claimed to be superior to Ac in both chronic and acute dialysis. We compared Ac and Bi dialysate in 30 acute patients during 120 dialyses. Four patients were diabetic and 2 had liver failure.

Patients were dialyzed alternating Ac and Bi dialysate in a double-blind cross-over manner, each patient was his own control. BUN, Cr, Na^+, K^+, Hct, osmolality, Δ osmolality, % ultrafiltration, arterial blood gases, pre, post and lowest dialysis mean arterial blood pressure (MAP), hypotensive episodes (BP↓>25%) and symptoms of hypotension were recorded.

There was no difference in pre-dialysis chemistries, osmolality, or osmolality fall, changes in MAP or hypotensive episodes, symptoms of hypotension and ultrafiltration. PCO_2 and pH were slightly lower in the acetate group at the second hour but not at end of dialysis. Four patients had acetate determinations, all metabolized acetate normally.

Mean ± SD:	MAP mmHg		BP↓	Δ UF	Δ Osm
	Pre	Max.Fall	>25%	% BW	mOsm/kg
Ac:	95.5±20.0	17.5±11.2	11.6	1.6±1.5	14.1±9.0
Bi:	98.1±19.8	20.5± 9.4	19.1	1.9±1.5	10.9±8.8
P :	>.1	>.1	>.1	>.1	0.056

These findings contradict recent suggestions that severly ill patients should not be dialyzed against acetate. Since acetate is technically much easier to use and has no clinical drawbacks, it does notneed to be replaced with Bi in acute patients. Other factors must be more important than acetate in generating hypotension during acute dialysis.

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD): NITROGEN BALANCE IS MAINTAINED OR IMPROVED DURING INITIATION OF THERAPY. M. Brzostowicz, P. Schoenfeld, G. Kaysen, D. Mapes,* Y. Newhouse, L. Piercy, and M. Humphreys. Univ. of Calif. Renal Center, San Francisco General Hosp., San Francisco, CA.

Because of continuous significant protein loss with CAPD, concern exists that not all patients are able to maintain nitrogen balance. We studied 7 stable ESRD patients (6 previously treated with hemodialysis, 1 with intermittent PD) on a metabolic ward during the initial 14 days of CAPD therapy. Diets were designed to reflect the patients' usual nutritional intake, but were constant in each patient during the period of study. Protein intake ranged from 0.8 to 2.0 ($\bar{x}$= 1.4±.4) gm/kg/d, and total energy intake (dialysate glucose + diet) from 26 to 64 ($\bar{x}$= 40±13) kcal/kg/d. Two patients were insulin dependent diabetics. Four patients were clinically well-nourished and were at or above desirable body weight (BW); 3 were either clinically malnourished or below desirable BW. Measurement of arm muscle circumference (AMC) in the two groups of patients showed significant differences (111±7.8 vs 89.2±7.2% of standard) $p<.02$. Nitrogen balance studies showed that despite variable protein and energy intake, all 4 well-nourished patients maintained net nitrogen balance while 2 of 3 malnourished patients developed positive nitrogen balance and gained weight during the study period.

We conclude that negative nitrogen balance does not develop during initiation of CAPD in spite of prodigious dialysate protein losses ($\bar{x}$= 14.6±3.8g/d) even if patients are malnourished. Well-nourished patients maintain zero nitrogen balance appropriately and malnourished patients may achieve positive nitrogen balance and gain weight.

AUTOMATED LONG CYCLE PERITONEAL DIALYSIS (ALCPD). Fred F. Adams, Joel R. Brunt*, C. Thomas Tucker*, and Arthur V. Williams. Charleston VAMC and Medical University of S.C., Charleston, S.C.

ALCPD is a treatment modality which uses the advantages of a cycler PD system to provide the therapeutic efficacy of low clearance, long dwell dialysis, which previously was available only as continuous ambulatory PD (CAPD). ALCPD uses a modified PD cycler (delivering preheated dialysate, and allowing variation of cycle frequency, exchange volume and dextrose concentration) to provide nighttime dialysis, with a single connect-disconnect. Three to four 2 L. exhanges are cycled each night (2½-3½ hr. dwell). A final 2 L. exchange, instilled prior to disconnection in the morning, is left to dwell 12 hours during the day. We have hometrained 6 patients to use ALCPD. Each patient has been afforded improved appetite and sense of well-being, greater dietary freedom, and enhanced blood pressure, volume and biochemical control. Four patients were easily converted from other PD regimens. Because the cycler is used in stabilization therapy, hometraining in the 2 new patients was begun at catheter insertion, facilitating transition to ALCPD. Its use in hospitalized or disabled home PD patients, with minimized need for partner assistance and its provision for conversion to rapid lavage therapy for peritonitis, further exemplify the advantages and flexibility available with ALCPD. Thus ALCPD provides an effective PD alternative, and the potential for wider application of low clearance, long dwell dialysis than does CAPD. At the same time, when ALCPD and CAPD are used interchangeably, the patient can be provided the advantages of both and a therapeutic versatility unavailable with either technique alone.

SURPRISINGLY HIGH HEMATOCRIT (HCT) DURING MAINTENANCE HEMODIALYSIS (MH). G. Charles, A.P. Lundin III, T. Manis, B. G. Delano, T. Joshi, T.K. S. Rao, E.A. Friedman. Downstate Medical Center Brooklyn, N.Y.

Anemia is a universal component of chronic uremia. We identified a subset of MH patients with normal HCT and explored this finding. The records of 549 MH patients at 5 facilities were reviewed to determine the prevalence of a mean HCT≥ 40% on 3 determinations over 3 months. Eleven patients (2.0%), 8 men and 3 women, of mean age 48.6± 15.4 yrs. (26 to 72) on MH for a mean of 68± 41.7 months (10 to 132) had a mean HCT% of 42.6± 3.3% (40 to 50%). The charts of these 11 patients were analyzed to discern possible contributing factors.

All patients had been anemic when MH was begun. No obvious cause of erythrocytosis was discovered though 2 patients had polycystic disease. In all of those tested (9 of 11) O_2 saturation of hemoglobin exceeded 90%. Androgenic steroids are currently administered to 6 of 11. Peripheral venous blood platelet and leukocyte counts were normal in all 11. Parathyroid hormone (PTH) was high in 8 of 9, mean 867± 711 pg/ml (range 286 to 2200) (normal 163 to 347 pg/ml). One unilaterally nephrectomized patient whose PTH was 2200 pg/ml maintains a mean HCT of 47%. Only 1 of 11 voids any appreciable quantity of urine. No patient had been a renal allograft recipient nor had any ever received a blood transfusion. The clinical course during MH of high HCT patients was not remarkably dissimilar from the overall group whose mean HCT was 27%.

We conclude that a small (2%) proportion of MH patients can have normal HCT. The responsible mechanism(s) is unknown.

THE EFFECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD) ON PARATHYROID HORMONE (PTH) AND MINERAL METABOLISM. J. Delmez, E. Slatopolsky, K. Martin, B. Gearing,* and H. Harter, Washington Univ. School of Medicine, St. Louis, Missouri, USA

CAPD has the potential to offer improved control of mineral homeostasis compared to chronic hemodialysis (CHD). Ten CAPD patients using standard dialysate solutions containing 7.0 mg/dl of calcium (Ca) and 1.8mg/dl of magnesium (Mg) were evaluated. Utilizing a C-terminal antibody assay, which measures both intact hormone and C-terminal fragments, it was found that the mean clearance of PTH was 1.5±.73ml/min (SEM) yielding a daily net removal of 13.6±3.2% of estimated total extracellular PTH. Gel electrophoresis of the dialysate revealed the presence of both intact PTH and fragments in approximate proportions as those found in serum. Normal levels:25-(OH) vitamin D_3 and vitamin D binding protein (DBP) (25.8 ±6.5ng/ml and 545.8±86.9ug/ml) were observed prior to initiation of CAPD. Following 6 months of CAPD, the levels were unchanged. Timed dialysate collections (N=93) showed a net influx of Ca of 9.8±2.8mg with each 1.5% dextrose exchange but removal of 21.5 ±3.2mg with each 4.25% dextrose exchange resulting in a daily Ca influx of only 9.9±9.7mg. The daily removal of phosphorus (P) was 308.4±15.5mg. Despite elevated serum Mg levels in all patients the net daily removal was inadequate (31.2±15.5mg). We conclude: 1) Unlike CHD, CAPD removes significant amounts of PTH. 2) Normal 25-(OH) D_3 and DBP levels are maintained with CAPD despite large protein losses. 3) Substantial amounts of P are removed with CAPD but not to an extent that precludes use of P binders. 4) Dialysate containing higher Ca and lower Mg concentrations should be made available to improve mineral homeostasis.

CONTINUOUS CYCLIC PERITONEAL DIALYSIS (CCPD). Jose A. Diaz-Buxo, Phillip J. Walker, Charles D. Farmer, Joe T. Chandler, Kenneth L. Holt. Nalle Clinic Kidney Center, Charlotte, N.C.

Among the virtues of CAPD figure the steady state provided by its continuous nature, effective clearances of larger molecules and lower cost. However, the relatively high incidence of peritonitis due to multiple connections, often in inconvenient places, and the interruption of daily activities has limited its use. CCPD requires only one connection at night and one in the morning. The cycler is programmed to deliver 3 or 4 exchanges of 2L each over 9 or 10 hours. At disconnection in the morning, 2L remain in the peritoneal cavity for 14 hours. Clearances obtained in 3 patients during a 16 patient-month experience show values comparable to CAPD and superior to intermittent peritoneal dialysis (IPD).

	CCPD	CAPD	IPD	HD
Urea	66.7	76	60	135 (L/week)
Creatinine	57.7	58	28	90
B_{12}	44.9	50	16	30

Diets were liberalized due to CCPD's ability to ultrafilter and remove potassium. CCPD incorporates continuous dialysis with long dwell times and the convenience of a cycler for nocturnal exchanges, allowing the patient to enjoy a full day of uninterrupted activity and a 9 hour sleep while receiving dialysis. It should significantly reduce the incidence of peritonitis due to its less frequent connections (40% of CAPD) performed in a controlled environment, and competes economically with all other modalities of therapy.

PROTEIN AND BACTERIAL REJECTING FILTERS FOR PERITONEAL DIALYSIS. Dhein, CR*, Thornhill, JA*, Chiosi, C*, Ash, SR. Hemodialysis Laboratory and Small Animal Clinic, Veterinary School, Purdue University, West Lafayette, IN

Peritoneal dialysis is gaining in popularity because of its simplicity and its slow but effective removal of uremic toxins. However, protein loss and bacterial infection are still major drawbacks. A protein and bacterial rejecting filter would obviously solve these problems of peritoneal dialysis, but in unidirectional flow, peritoneal fluid tends to quickly clog any such filter. Two filters have been obtained with supported membranes allowing bidirectional flow: the 0.2 M^2 Amicon XM 50 hollow fiber Diafilter, and the Millipore GLC 100, 0.22 micron filter. Utilizing recirculation of peritoneal fluid through the hollow fibers of the Amicon filter, the high shear rate was produced within the hollow fibers of the Amicon filter, and a bidirectional flow of 80 to 100 ml/min was produced for peritoneal fluid and dialysate. In animal tests of normal dogs, however, flow rate decreased as protein content of the peritoneal fluid increased above 100 milligram %. Using the GLC 100 filter, 1 meter hydrostatic pressure head (gravity flow) allowed peritoneal fluid to flow at 150-230 ml/min and dialysate to flow at 100 ml/min, bidirectionally across the filter. These flows were reproducible in dialysis of normal dogs, for up to 3 weeks, using 2L exchanges. The filter was challenged with E. Coli during the tests, and rejected 100% of the organisms. Clinical tests are now being performed with both CAPD and IPD patients.

CONTRASTING ALTERATIONS IN OXYGEN CONSUMPTION ($\dot{V}O_2$) AND RESPIRATORY QUOTIENT (RQ) DURING ACETATE (A) AND BICARBONATE (B) HEMODIALYSIS (HD). A.R. Eiser, D. Jayamanne* , C. Koksong*, H. Che*, R.F. Slifkin and M.S. Neff, City Hospital Center at Elmhurst and Mt. Sinai School of Medicine, New York, N.Y.

During A HD, PaO_2 falls significantly while during B HD there is little or no drop in PaO_2. We measured alterations in $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$ during 7 A and 7 B HD. The results summarized below depict changes from pre dialysis values.

		$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}CO_2$	RQ
A HD	Mean Δ	-1102*	+61.4*	-37.6*	-.50
	± SEM	341	19.3	11.1	.13
	P	<.02	<.02	<.02	<.01
B HD	Mean Δ	- 747*	-45.6*	-21*	+.18
	± SEM	246	17.8	10.4	.07
	P	<.05	<.05	NS	<.05

*cc/min STPD

$\dot{V}O_2$ increased during A HD but decreased during B HD with respect to baseline measurements and conversely RQ decreased during A HD but rose during B HD. When $\dot{V}O_2$ and RQ during A HD are compared to $\dot{V}O_2$ and RQ during B HD, the differences are very significant ($p < .001$). We conclude that differences in PaO_2 during A and B HD are the result of contrasting changes in RQ during A and B HD resulting from opposite changes of $\dot{V}O_2$. Dialysance of CO_2 does not account for the fall in PaO_2 during A HD, since $\dot{V}_E$ and $\dot{V}CO_2$ decreased similarly in A and B HD, and $\Delta\dot{V}O_2$ was the factor accounting for differences in RQ. Oxygen is consumed during A metabolism and this may account for differences in $\dot{V}O_2$ during A versus B HD.

SEVERE HYPOPHOSPHATEMIA (hPO_4) FOLLOWING PERITONEAL DIALYSIS IN TWO DIABETICS. D.J. Farley,* B.T. Thompson,* B.R. Bistrian,* J.A. D'Elia, and A. Kaldany. Joslin Clinic Renal Unit, N.E. Deaconess Hospital and Harvard Medical School, Boston, Mass.

Severe iatrogenic hPO_4 has been reported with number of therapeutic maneuvers such as intravenous hyperalimentation. We report two cases of severe hPO_4 following peritoneal dialysis (PD) in two diabetics on PD who developed staphylococcal peritonitis. Both patients had normal serum PO_4 prior to their last PD.

	Case #1	Case #2
Age (years)	38	80
Duration of Diabetes (years)	20	20
Insulin Therapy	yes	no
Duration of PD (months)	14	10
Admission Diagnosis	peritonitis	peritonitis
Antibiotic Therapy	yes	yes
Last PD Data:		
No. of PD Exchanges	50	30
Dialysate	4.25%	1.5%
Insulin in Dialysate	750U	none
Insulin S/C	190U	none
Post PD Glucose	672 mg/dl	312 mg/dl
Post PD Ca	9.6	9.2
Post PD PO_4	0.9	1.8
Post PD Art. pH	7.30	7.41

The association between PD and severe hPO_4 has not been previously reported. It is unlikely that a significant external PO_4 loss occurs in PD. Yet, in two cases with peritonitis, severe hPO_4 was observed with irreversible neurological damage. While the exact mechanism is still unclear, it may be prudent to monitor the serum PO_4 of patients with peritonitis, undergoing PD.

NET SODIUM FLUX (J) IN POST-DILUTION HEMOFILTRATION (HF) AND HEMODIALYSIS (HD). Frank A. Gotch, R.K. Davies Medical Center, San Francisco, CA.

Intra and inter treatment morbidity are decreased by HD with increased dialysate Na (C_DNa) and by HF. Therefore it is crucial that studies comparing HF to HD be designed to assure equal J. With similar net QF, the Na concentration gradients (ΔC_{Na}) blood→dialysate and blood→replacement fluid determine J in HD and HF. A first order Na transport model with osmotic distribution Na equal to total body water has been used to evaluate plasma protein concentration (C_p) dependent Donnan forces and determine effective ΔC_{Na} in HD from pre and postdialysis serum Na. Clinical data simulating HF was obtained with isolated ultrafiltration in cellulose acetate dialyzers with Q_B 100 ml/min and filtration fraction (FF) = .40. The effective aqueous blood Na concentration was defined as $\alpha \cdot C_BNa$ where α = 1/Donnan Ratio. The dependence of α on $\overline{C_p}$ in the dialyzers, gm/dL, was $\alpha = 1.010 - .009\overline{C_p} \pm .020$ (95% confidence), N = 33. The ↑ $\overline{C_p}$ in HF requires that C_DNa be higher than replacement fluid Na (C_RNa) to assure equal J in HD and HF. The data indicate that for J in HD to equal that for HF with C_RNa = 140mEq/L and FF decreasing from 0.60 to 0.40 over 4 hrs, the C_DNa should be decreased from 147 to 143 over a 4 hr HD. Since in many HD/HF studies $C_DNa \leq C_RNa$, these results suggest greater Na removal in HD than in HF and ↓ morbidity in HF may be dependent on relative Na rather than middle molecule removal. In pre-dilution hemofiltration this would not apply.

LACK OF EFFECT OF PROSTAGLANDIN E_2 (PGE_2) OR ARACHIDONIC ACID (AA) ON PERMEABILITY OF THE RABBIT PERITONEUM IN VITRO. P. Mitchell* and P.U. Feig, Univ. Conn. School of Med., Farmington, CT.

The effect of drugs on solute clearance can be studied in vitro in order to determine the permeability coefficient (K) without the drugs' effects on blood flow, convection or membrane area.

K for urea (K_U), creatinine (K_C), and glucose (K_G) were determined in membranes placed in Ussing chambers over three consecutive 30-min. periods: Period I served as control; periods II and III were either control (n = 12) or experimental, with 1.5 μg/ml PGE_2 (n = 14), or 50 μg/ml AA (n = 10).

Results (mean ± SD) were (K in 10^{-4} cm/sec):

	Control			PGE_2			AA		
	I	II	III	I	II	III	I	II	III
K_U	2.24	2.20	1.93	1.54	1.60	1.76	1.87	1.60	1.62
	.69	.82	.73	.69	.61	.80	.61	.58	.60
K_C	1.33	1.25	1.24	1.30	1.18	1.21	1.35	1.23	1.33
	.54	.57	.53	.53	.53	.53	.29	.59	.58
K_G	1.03	.99	1.08	1.01	1.14	.94	1.07	1.09	1.28
	.52	.42	.51	.49	.55	.35	1.10	.38	1.02
$\frac{K_C}{K_U}$	.73	.76	.90	.90	.73	.73	.76	.75	.83
	.03	.15	.30	.29	.17	.20	.17	.26	.24
$\frac{K_G}{K_U}$	.60	.55	.76	.71	.70	.61	.59	.72	.73
	.13	.07	.07	.34	.20	.23	.17	.23	.29

K_U, K_G, K_C, and the ratios K_C/K_U and K_G/U during periods II and III were not significantly different from period I.

We conclude that over a 60-min. period, pharmacologic concentrations of PGE_2 and AA have no effect on small solute K in the rabbit peritoneum.

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD) IN UREMIC RABBITS: A RELIABLE ANIMAL MODEL. L. Gotloib*, P.Crassweller*, H.Rodella*, G.Zellerman*, R.Ogilvie*, V.Calderaro*,L.Brandes*, and D.G. Oreopoulos. Toronto Western Hosp. Toronto, Canada.

The increased interest in CAPD necessitated the development of an animal model in which the various aspects of CAPD could be studied. We describe a technique developed in uremic rabbits. Fifteen rabbits were made chronically uremic by two steps removal of 92% of their kidney mass. As controls we used a group of 11 intact animals and 11 animals with bilateral nephrectomy. Three months after partial nephrectomy, BUN was 72.0±20.1 mg% ($\bar{x}$±S.D), creatinine 5.5±1.1 mg%, and Hct 28.6±2.5 %. CAPD was performed over a 2 week period through a specially designed peritoneal catheter and a modified cycler adjusted to deliver 300 ml. of dialysate every 6 hours. To avoid catheter blockage and clotting of the effluent,the animals underwent omentectomy before catheter implantation and we were adding 20,000 units of heparin per litre of dialysate. On CAPD the anephric group showed a high mortality (63.6%) mainly due to overhydration. In contrast only one of the partially nephrectomized and none of the intact animals died. All animals on CAPD showed significant protein losses and a simultaneous marked decrease in their plasma protein and body weight. In the uremic group, CAPD resulted to a decrease in BUN and serum creatinine. The described model is reliable and reproducible and will be useful in carrying out metabolic studies especially those related to protein losses, and lipid abnormalities as well as their prevention and long term consequences.

COMPARISON OF PROSTACYCLIN (PGI) AND HEPARIN (H) ON HEMODIALYSIS (HD) IN DOGS. M. Gross*, H. Bush* and W. Flamenbaum. Departments of Medicine and Surgery, Boston VA Medical Center, Boston, MA.

The study was performed on 6 uremic dogs to compare the efficacy of PGI and H as anti-coagulants during HD. Dogs were made uremic by bilateral ureteral ligation, and were dialyzed via an arteriovenous shunt under anesthesia. PGI was infused continuously into the arterial limb of the dialyzer (100 ng/kg/min) while H was administered as a 5000 unit bolus at the beginning of dialysis. Each dog served as its own control. PGI and H were alternated and a total of 4 dialyses/dog were performed. Parameters followed to assess the efficacy of dialysis included: dialysance (D,ml/min) of urea (u) and creatinine (c), ultrafiltration rate (ufr, ml/hr) residual volume (RV, ml) and platelet count (PC, %of baseline). A more stable PC and better UFR were observed with PGI.

	D_u	D_c	UFR	RV	PC
H	73±12	61±10	308±36	8.5±5	51±14
PGI	72±12	61±11	368±56*	9.8±6	80±24*

(*Significantly different from H, $P<0.025$)

In conclusion, PGI alone can be used as an effective anti-coagulant. In contrast to H it maintains the PC and improves the UFR during HD. At the dosage employed PGI does not appear to increase the efficacy of dialysis as judged from D_u and D_c.

THE RELATIVE EFFECT OF LEUKOPENIA AND DIALYSATE COMPOSITION ON THE DIALYSIS-ASSOCIATED HYPOXEMIA. R. M. Hakim* and E. G. Lowrie. Harvard Medical School and The Kidney Center, Boston, MA.

The relative effect of dialysate base composition (acetate or bicarbonate) and dialyzer-induced leukopenia on the dialysis-associated hypoxemia was studied in 8 chronic hemodialysis patients. Each patient was dialyzed randomly with a cellulosic-type membrane dialyzer (Cordis-Dow 1.3) HFK and with a polymethylmethacrylate (PMMA) membrane dialyzer (Toray B-2-M). Previous studies have shown significant differences in the leukopenia induced by these two membranes. With each type of membrane, the dialysate base was alternately acetate or bicarbonate. Other dialysate factors, such as sodium and potassium concentrations, were held constant.

Blood gases were measured at the initiation of dialysis and at 15, 30, 60, 120 and 180 minutes. A multivariate analysis of the data showed statistically significant difference in the hypoxemia between dialyzers ($p< 0.05$) and dialysate ($p< 0.001$) such that the maximum hypoxemia was observed when patients used the cellulosic-type dialyzer in association with acetate (decrease in PO_2 to 75% of initial value at 60 minutes) and the least hypoxemia was seen when the same patients used the PMMA type dialyzer in association with bicarbonate dialysate (decrease in PO_2 to 95% of initial value at 30 minutes). Furthermore, with the use of bicarbonate, the PO_2 returned to baseline value within 3 hours, while the use of acetate in the dialysate was associated with a sustained hypoxemia. Our results thus suggest that the dialysis-induced hypoxemia is related to both the severity of leukopenia induced by different membranes as well as the dialysate base composition.

REHABILITATION STATUS OF 2,481 AMERICAN MAINTENANCE DIALYSIS (MD) PATIENTS. Robert A. Gutman, William W. Stead and Roscoe R. Robinson. Duke Univ. Medical Center, Durham, North Carolina.

Little information is available regarding either the current physical activity or employment of American MD patients. We surveyed 18 dialysis centers in several regions of the country who reported on over 95% of their patients. The average age was 50± 15 (SD) years; 55% male; 55% white; and 12% of the group were diabetic (dia). The average duration of dialysis was 2.7±2.6 years. Physical activity status was assessed according to the Karnofsky scale (KS) and the scores aggregated into 4 broad groups. Employment status was categorized into 3 areas. Both groupings are expressed as percent of the identified groups of patients:

PERFORMANCE STATUS				
	Moribund	Debilitated	Self care	"Rehabilitated"
KS %	1-39	40-69	70-79	80+
Diabetics	8	47	25	23
Non-dia	2	18	21	60
<age 60	1	12	19	68
>age 60	3	32	26	40

EMPLOYMENT STATUS			
	Unemployed	Homemaker	Employed
Diabetics	57	29	12
Non-dia	43	31	25
Men, age 21-59	58	16	26
skilled	32	14	55
>12th grade	27	8	65

These and similar data from this multi-center survey provide a quantitative assessment of the current degree of rehabilitation of American MD patients.

ACUTE RESPIRATORY ACIDOSIS (RA) - A POTENTIAL COMPLICATION OF SORBENT REGENERATIVE HEMODIALYSIS. L. Lee Hamm* and Thomas D. DuBose, Jr. Univ. of Texas Hlth. Sci. Ctr., Dallas, Tx.

Bicarbonate hemodialysis (BHD) offers several advantages over standard acetate dialysis (AcHD) for critically ill patients. The sorbent regenerative system (REDY®) is a convenient and widely employed method of BHD and AcHD. In contrast to standard dialysis, REDY has been associated with CO_2 production, but the acid-base derangements resulting from this process have not been evaluated. After observing severe RA (PCO_2 = 80 mm Hg) in a mechanically ventilated patient during REDY BHD, we prospectively evaluated acute acid-base parameters in 15 stable renal failure patients during 30 REDY dialyses. Dialysate and venous blood line PCO_2 was markedly elevated early in BHD and late in AcHD with hollow fiber dialyzers (HF). In the first hour of BHD with HF, dialysate PCO_2 consistently exceeded 230, falling only slightly (169 mm Hg) at 4 h. Significant mass transfer of CO_2 from dialysate to venous blood was demonstrable (venous PCO_2 = 181.9 ± 24.1) and resulted in a marked diminution in venous pH (7.06 ± 0.07). Similar findings were observed during AcHD after 2 h. Despite the addition of CO_2 to venous blood, arterial PCO_2 remained unchanged during both AcHD and BHD in these stable patients. Dialysate and venous PCO_2 was normalized with coil dialyzers by aeration of the dialysate. The magnitude of CO_2 generated by the REDY is sufficient to cause severe RA in patients with respiratory impairment during dialysis with noncoil dialyzers. The potentially deleterious hemodynamic effects and/or electrolyte disorders due to mass transfer of CO_2 from dialysate to blood deserve further investigation.

PSEUDOMEMBRANOUS COLITIS AND CLOUDY PERITONEAL DRAINAGE IN PATIENTS ON PERITONEAL DIALYSIS. S. Paul Handa, S. Greer *, and H.D.Tewari *, Saint John Regional Hospital, Saint John,New Brunswick, Canada.

Causes for peritonitis during peritoneal dialysis include bacterial or fungal infections, endotoxic and chemical irritants in the dialysate, but aseptic peritonitis secondary to inflammation in the colon has not been described before. In our 38 patients maintained on peritoneal dialysis (27 IPD and 11 CAPD)for an average 9 mos.(1-23mos), there were 50 episodes of cloudy drainage (23 gram +ive 10 gram -ive, 1 Fungal and 16 Aseptic).

Three patients with aseptic cloudy drainage, presented with Pseudomembranous Colitis(PMC): watery diarrhoea, abdominal cramps, pyrexia and weight loss.Hyponatremia and hypoalbuminia were seen in each case.Diagnosis of PMC was made on sigmoidoscopy and tissue biopsy.Cytotoxicity assays on stools were not carried.

One patient remained toxic, and moribund. Other two,however, recovered. In one patient Cholestyramine and Vancomycin were used and she has been asymptomatic since then. The improvement in cloudy drainage corresponded to recovery of Pseudomembranous Colitis;suggesting the role of Clostridia difficile toxins in the pathogenesis of cloudy drainage.

In conclusion, the appearance of cloudy drainage in a clinical setting of diarrhoe in patients on peritoneal dialysis may suggest an associated Pseudomembranous Colitis. The condition is reversible but in an occasional patient, it can add severe metabolic dysfunction in uremia.

● PREVENTION OF DIALYSIS HYPOTENSION: A COMPARISON OF PROTECTIVE MANEUVERS. W. Henrich, T. Woodard*, W. Pettinger*, J. Nixon*, R. Cronin, and J.McPhaul. VAMC and UTSW Med Sch, Dallas, Texas.

Hypotension is a common and limiting complication of routine dialysis therapy. To determine the relative efficacy of several practical maneuvers used to prevent dialysis hypotension, we compared the orthostatic mean blood pressure response (TILT$\bar{x}$BP) of 8 stable dialysis patients to a 2.5% weight reduction after 2 hours of the following: Regular Dialysis (RD), Ultrafiltration (UF), High Sodium Dialysis (HNa), and 25% Hypertonic Mannitol (HMAN). The sequence of maneuvers was randomized, and plasma osmolality (OSM), norepinephrine (NE) and cardiac output (CO) were also measured before and after each maneuver:

	TILT$\bar{x}$BP (mmHg)	TILT NE (pg/ml)	Pre/Post OSM (mOsm/kg)	Pre/Post CO (L/min)
RD	87→63*	529→697*	337→316*	4.8→3.6*
UF	84→88	562→643	334→333	3.9→4.3
HNa	87→81	436→628*	334→327*	4.5→3.8*
HMAN	89→79	495→642	332→325*	4.3→3.6*

*p<.05

The reductions in plasma volumes were similar with each maneuver. These results identify UF as the most effective antihypotensive dialysis therapy, although HNa and HMAN clearly improved orthostatic tolerance to weight loss. Further, this protective effect of UF correlates best with constant OSM and may be dissociated from any change in plasma NE levels. Finally, the resistance to orthostatic hypotension and better maintenance of CO after UF compared to HNa and HMAN suggests that OSM may have an independent effect on cardiac preload and myocardial contractility.

MANNITOL INDUCED DIARRHEA FOR EXCESSIVE WEIGHT GAIN IN MAINTENANCE HEMODIALYSIS (MD) W.F. Heneghan, J. Feldman, A.P. Lundin, E.A. Friedman. Downstate Medical Center, Brooklyn, New York.

To test the feasibility of using the GI tract for fluid removal in volume expanded maintenance hemodialysis patients we administered mannitol orally to induce diarrhea acutely. A total of 7 studies in 6 fluid overloaded MD patients were performed. Mannitol, a hexahydric alcohol, was given in a 20% or 25% water solution over 1 hr. in a total dose of 125 to 200g (mean 159g). Nonpainful diarrhea began within 1 1/2 hrs. in 6 to 7 treatments, and after 6 hrs. in one patient. Diarrheal stools were pooled and the filtered supernate was analyzed for Na, K, and creatinine content. Patients lost weight (mean 2.1Kg, range 0-3.1Kg) after passing a mean diarrheal stool of 2.8Kg (range 0-3.3Kg). Blood urea nitrogen (71.7mg/dl pretreatment) and serum creatining (15.5mg/dl pretreatment) concentrations were stable post diarrhea with changes of -4 to +8mg/dl and -3.6 to +2.8mg/dl respectively. The diarrheal stools contained a mean Na content of 46.8mEq (range 27 to 63mEq) and a mean K content of 12.4mEq (range 4.3 to 31mEq). Plasma electrolytes showed an increase in Na (1.7mEq/l) and K (0.7mEq) and a decrease in CO_2 (2.1mEq). Patients tolerated rapid ingestion of mannitol well though the limiting factor was emesis which occurred in 5 of 7 trials until the rate of administration was reduced. One patient who had prompt resolution of pulmonary edema requested further mannitol treatments rather than extra hemodialysis. We conclude that MD patients with excessive weight gain between dialyses could use the gut for water extraction, but the side effect of vomiting requires control by adjustment of rate and concentration of ingestion of mannitol.

STABILITY OF PERITONEAL TRANSPORT AFTER INHIBITION AND STIMULATION OF PROSTAGLANDINS. P. Hirszel*, M. Lasrich* and J.F. Maher, Depts. Med., U. Connecticut Hlth. Ctr., Farmington, CT and Uniformed Serv. U. Hlth. Sci., Bethesda, MD

Peritoneal clearances (C) respond as predicted to vasoactive drugs and to local prostaglandin (PG) instillation. To test effects of endogenous PG on C in health, we compared control dialyses in 10 alert New Zealand white rabbits fed ad lib to dialyses after PG synthetase inhibition by indomethacin (I) or stimulation of PGI_2 by sulfinpyrazone (S). In our dialysis model we measure dialysate volume (V) by isotope dilution and C by concentration ratio x V/t. Control C of creatinine (cr) and urea corrected to a constant intraperitoneal dwell time were 0.66 and 0.76 ml/kg/min, respectively. After I 5.0-5.7 mg/kg p.o. for 5 d (which inhibited platelet aggregation) mean C were cr 0.71 and urea 0.95 ml/kg/min ($p>0.05$ vs bracketed controls) and after 10.0-12.5 mg/kg for 3 d were 0.62 and 0.71 ml/kg/min ($p>0.3$). Osmotic (1.5% dextrose) water flux did not change ($p>0.3$) from control 0.20 ml/kg/min. S did not change C cr or urea (0.48 and 0.66 ml/kg/min after 10.0-11.4 mg/kg p.o. for 6 d, $p>0.05$, 0.66 and 0.86 ml/kg/min after 20.0-21.4 mg/kg for 6 d, $p>0.05$ and 0.67 and 1.00 ml/kg/min in 2 with 30 mg/kg/d). Osmotic water flux did not change ($p>0.05$). Stability of mean C after I or S was not due to dominant vasoconstrictor PG effects in some rabbits and vasodilator in others since deviations from control (ignoring direction) were no more than variance in controls ($p>0.05$). Stability of peritoneal C after modifying PG like our prior observation of stability after infusion of PGI_2 implies no preferential mesenteric blood flow distribution, unlike significant changes we reported previously after local instillation of PGE_2 or $PGF_{2\alpha}$

PERITONEAL FLUID EOSINOPHILIA DURING THE FIRST MONTHS OF MAINTENANCE PERITONEAL DIALYSIS. H.M. Humayun*, T.S. Ing, V.C. Gandhi, W.T. Chen, J.E. Hano and J.T. Daugirdas*. Veterans Administration Hospital, Hines; Loyola University School of Medicine, Maywood; Illinois.

Last year (ASN 1979, Humayun et al.) we reported a high prevalence of peritoneal fluid eosinophilia (PFE) among maintenance peritoneal dialysis (MPD) patients. PFE was defined to be present when eosinophils represented at least 10% of total non-erythrocyte cells in a pre-dialysis specimen, provided that the absolute peritoneal fluid eosinophil count was at least 40 per mm^3. Further follow-up has revealed 3 clinical patterns. The vast majority of patients developed PFE during the initial months of peritoneal dialysis. In all such patients (12) followed for longer than 6 months, PFE resolved after 1 to 5 months of MPD. In 2 other patients, PFE occurred during the treatment phase of bacterial peritonitis. Finally, in 2 other patients, PFE was a chronic condition, persisting for the duration of follow-up (6 months to 2 years).

Although absolute peritoneal fluid neutrophil counts were often over 200 per mm^3 during periods of PFE, there was no response to antibiotic therapy, and cultures of the peritoneal fluids were always sterile.

Our data suggest that PFE most frequently occurs during the early months of MPD. It is usually a self-limited condition and requires no treatment. The etiology remains unknown.

TREATMENT OF REFRACTORY HEMODIALYSIS ASCITES WITH MAINTENANCE PERITONEAL DIALYSIS. T.S. Ing, J.T. Daugirdas*, S. Popli, A.O. Kheirbek*, H.M. Humayun*, and V.C. Gandhi. Veterans Administration Hospital, Hines, Illinois.

Five maintenance hemodialysis patients developed ascites that was refractory to treatment by ultrafiltration during dialysis. Use of isolated ultrafiltration either precipitated side effects, or else required prolongation of treatment time, which patients declined to accept. Diagnosis of hemodialysis ascites was established by exclusion after a careful evaluation for other possible etiologies had been carried out.

After treatment with maintenance peritoneal dialysis, ascites resolved promptly in each case. Three patients experienced a dramatic improvement in appetite as well as an increase in dry weight. The 5 patients have now been followed for 6 to 54 months, and ascites has not recurred. Serum albumin levels decreased from a mean of 3.4 Gm./dL. to 2.5 Gm./dL. after initiating maintenance peritoneal dialysis. However, 6 months later, albumin levels had risen to 3.1 Gm./dL., despite continued peritoneal dialysis. Serum total protein levels showed a similar early decline from 6.8 to 5.5 Gm./dL., followed by improvement and stabilization at a mean value of 6.4 Gm./dL.

The results suggest that maintenance peritoneal dialysis is a useful therapeutic alternative in the treatment of refractory hemodialysis ascites.

●HISTOLOGY IN DIALYSIS OSTEOMALACIA (OM) SECONDARY TO ALUMINIUM TOXICITY. B. Ihle*, M. Buchanan*, R. Plomley*, B. Stevens*, A.d'Apice and P.Kincaid-Smith. Dept. of Nephrology, Royal Melbourne Hosp. and R.M.I.T., Melbourne, Australia.

Aluminium (Al) continues to be a major factor in the morbidity and mortality of chronic dialysis(CD) patients and the recommended maximum water conc.is becoming more stringent; presently 50µg/l. We prospectively looked at bone Al levels in 17 non-selected CD patients ($\bar{x}$42.5 months). Undecalcified sections were stained with aurin tricarboxylic acid which appears to be specific for Al. A control group (N=6) of non-uraemic autopsy specimens were also studied. Al and Ca were quantitated by atomic absorption spectrophotometry on dry specimens and expressed as Ca/Al ratios.

The control group was -ve on the histochemical (HC) stain and had Ca/Al ratio of $\bar{x}$ 8.78 ± 0.50 (S.E.M.). The CD group had $\bar{x}$ of 0.40 ± 0.03. There was no difference in the ratio between those HC +ve (N=8) and those not (N=9). The +ve HC group showed an intense red stain at the mineralization front (presence of Al confirmed by x-ray diffraction analysis) and differed from the HC -ve group by showing little or no biochemical (iPTH), x-ray or histological evidence of hyperparathyroidism (HPT) and a marked tendency to hypercalcaemia with no or very small doses of vit.D. The HC +ve group had predominantly OM while the HC -ve group showed either HPT alone or both. It is concluded that 1)Al in bone is high in CD patients exposed to non-treated water; 2)OM secondary to Al can occur early in CD; 3)Al can be identified by a specific HC technique; 4)Al associated OM is difficult to manage with vit.D therapy, and 5)these patients should be considered for early transplantation.

PREPARATION OF STERILE BICARBONATE-CONTAINING PERITONEAL DIALYSATE USING AN AUTOMATED DIALYSATE DELIVERY MACHINE. T.S. Ing, M.J. Quon*, J.T. Daugirdas*, V.C. Gandhi, and M.B. Epstein*. Veterans Administration Hospital, Hines; Christ Hospital, Oak Lawn; Illinois.

Bicarbonate-containing peritoneal dialysate may be useful in the treatment of lactic acidosis. We prepared such a dialysis solution by slightly modifying a BD Drake-Willock dialysate delivery machine. Under normal operation, two pumps operate in tandem to deliver product water and concentrate via tubings to a mixing chamber. We left the product water pump intact. The concentrate pump was fitted with two tubings, one of which conveyed an "acid" concentrate, and the other a "base" concentrate.

The "acid" concentrate contained appropriate amounts of sodium, calcium, magnesium, chloride, dextrose, and acetic acid. The "base" concentrate contained sodium bicarbonate. By rearranging the tubings leading from the concentrate pump, product water was allowed to mix with the acid concentrate first. The diluted acid concentrate solution then encountered the base concentrate further downstream.

In 4 separate experiments, product dialysate was found to contain 123 mEq./L. of sodium, 3.5 mEq./L. of calcium, 1.0 mEq./L. of magnesium, 94 mEq./L. of chloride, and 30 mEq./L. of bicarbonate. pH was less than 7.4, and the P_{CO2} was greater than 40 torr. Acetate level was calculated to be 3.4 mEq./L. Calcium and magnesium levels were closely similar in the final dialysate and in an ultrafiltrate of dialysate, suggesting that these cations were indeed in solution.

MYOCARDIAL (M) STRUCTURAL ABNORMALITIES OF MAINTENANCE HEMODIALYSIS (MHD) PATIENTS (P): DETECTION BY TWO DIMENSIONAL (2D) ECHOCARDIOGRAPHY (E). VK Jain, MS Rosenzweig*, NC Nanda*, RVM Cestero, Monroe Comm & Strong Mem Hosp, Univ of Roch, Roch, NY.

Thirty three stable MHD P underwent elective real time 2D E to look for cardiac abnormalities. E data were evaluated by 2 authors blinded to all clinical information. Adequate studies were obtained on 28/33 P. In 9/28 (Grp I) structural abnormalities seen as multiple, discrete, irregular, echodensities measuring 1 to 5 mm were detected in the myocardium of the ventricular (V) septum. Of these, 2P also had echodensities in left V posterior wall. Fluoroscopy in 4 Grp I P showed no M calcification in 3; 1 P showed calcification in the cardiac shadow but further localization was not possible. A thickened, echodense endocardium was seen in 6 of Grp I P and in 8 others(Grp II). Myocardium and endocardium were normal in the remaining 11/28 P (Grp III). Table below shows that Grp I P were on MHD longer, received more transfusions (T) and had significantly higher ($p<.02$) serum ferritin (SFt) levels.

	$\bar{x}$ Duration MHD	$\bar{x}$ Age	$\bar{x}$ T	$\bar{x}$ SFt ng/ml	#with LVH
GrpI	4.6 yrs	46.3	139±120	2946±1841	9/9
GrpII	3.6 "	49.5	90±113	1193±1439	8/8
GrpIII	3.0 "	48.6	58± 72	1381±1569	6/11

Etiology and significance of these previously undescribed abnormalities is unknown. Because left V hypertrophy (LVH) was widespread in all groups it probably cannot explain the echodensities. Preliminary fluoroscopy findings suggest that calcium deposition may not be involved. Degenerative changes such as fibrosis secondary to iron deposition may be implicated.

IN VITRO STUDIES ON SURFACE STERILIZATION OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS TUBING USING ULTRAVIOLET LIGHT. S.J.Joshi, J.Barnes‡ R.E.Duenkleberg‡ and J.Gidley*. Veterans Administration Medical Center, Saint Louis, Mo.

Continuous Ambulatory Peritoneal Dialysis(CAPD) is fast becoming a popular alternative to hemodialysis in the treatment of renal failure. Recurrent infections from contamination during bag and tubing changes, from microorganism on their surfaces, is a major problem with CAPD.

A box, which uses an ultraviolet light source for surface sterilization of these tubing connection sites, has been devised. The box is coated with reflective material on the inside. The tubing and connection is suspended in the cavity. The tubing is coated with a heavy,turbid culture of various organisms and exposed to ultraviolet light. Time taken to sterilize the surface is noted.

Organism	Strain/type	Time to kill
Candida albicans	-	10 min.
Staph aureus	ATCC 25923	5 min.
E.coli	ATCC 25922	5 min.

Bacteria inside tubing cavity were unaffected. Further studies with other organisms and mixed cultures are in progress.

Ultraviolet light sterilization may be a workable form of sterilization method for use in routine CAPD treatment.

SUCCESSFUL USE OF SELF-DIALYSIS (SD) IN A CHRONIC DIALYSIS PROGRAM. P.G. Jenkins, F.D. Gutmann, D. Mazumdar, R.E. Rieselbach, R. Bazylewicz.* University of Wisconsin (Milwaukee), Mount Sinai Medical Center, Milwaukee, Wisconsin.

Great differences of opinion exist as to the fraction of end stage renal disease (ESRD) patients (P) who might be able to perform SD. Our program is unique in that we offer only forms of SD, with P not willing or able to do SD referred to total care facilities. Our experience may reflect the optimal results possible for SD under the present ESRD program. Of 70 consecutive ESRD P cared for over the past 4½ yrs, only 9% were referred from other facilities for SD training. Of the 70, 21% did not do SD, 40% by choice, 60% for medical reasons. Of the 79% SD P, 44% did center SD, 56% home SD (11 peritoneal). Of 24 center SD, 12% went to total care units. Of 32 home SD, 9% went to total care units, 6% to center SD. Of center SD, 33% could have done home SD, while 67% had no helper.

	#	Male	Mean Age	Diabetes (DM)	Mortality (M)
Home	31	68%	50(23-73)	26%	21% (50% DM)
Center	24	58%	42(24-75)	13%	4%
Non-SD	15	47%	54(16-77)	27%	53% (50% DM)

Of the 70, 60% were men. SD was used by 83% of men and 71% of women. DM was present in 21% overall, 27% of non-SD P and 20% of SD P. M in DM SD P was 27%, in DM non-SD P, 100%. M in non-DM SD P was 9%, in non-DM non-SD P 36%. M in all non-SD P and P who left SD was 48% and in all SD P, 14%.

We conclude that probably 75% of all ESRD P can enter into some form of SD, with 45-50% doing home SD, and 25-30% center SD. Home helpers might significantly increase home hemodialysis use. M is very high in our non-SD P.

DIALYZABLE SERUM FACTORS AND INSULIN RESISTANCE OF UREMIA. A. Kaldany, K.L. George*, N. Abourizk*, D. C. Yoburn, D.G. Miller, U.A. D'Elia, and J.S. Soeldner*. Joslin Clinic Renal Unit, The E.P. Joslin Research Lab, Department of Medicine, N.E. Deaconess Hospital and Harvard Medical School, Boston, Mass.

The exact mechanism responsible for the insulin resistance of uremia is still unclear. In an effort to determine whether dialyzable serum factors may interfere with insulin receptor function, we have compared insulin binding and thymidine incorporation by healthy donor PHA-induced lymphoblasts, incubating in normal serum, pre-dialysis and post dialysis sera in 3 diabetics and 3 nondiabetics with chronic renal failure (CRF). Vigorous blastogenesis was obtained in all cultures as shown by stimulation indeces (SI) on Table I:

	Pre-dialysis Sera	Post Dialysis Sera
Non-Diabetics	44 ± 4.2	51.6 ± 5.6
Diabetics	33 ± 6.2	44 ± 8.1

(S.I. for Control Serum = 13)

Total insulin bound by lymphoblasts cultured in normal serum = 40.90 nM/10^6 cells. CRF data shown on Table II:

	Pre-dialysis Sera	Post Dialysis Sera
Non-Diabetics	4.09 ± 1.71	46.03 ± 6.78
Diabetics	2.06 ± 0.86	9.68 ± 3.35

The observed decrease of radiolabelled insulin binding to lymphoblasts cultured in diabetic sera may be explained by the competing presence of circulating non-labelled insulin and circulating anti-insulin antibodies with high affinity to the radiolabelled insulin. These data suggest that dialyzable uremic toxins may be responsible for the insulin resistance observed in uremia.

AMBULATORY BLOOD PRESSURE MONITORING IN HEMODIALYSIS PATIENTS. L.A. Katz, H.A. Greenblatt*, J.D. Dixon*, and S. Rubler*. Medical Service, New York VA MC, NYU School of Medicine, New York, New York.

Hypertension, an important cardiovascular risk factor in patients (pts.) on hemodialysis (HD), can be controlled by changes in dialysis regimen or drug therapy, only if the elevated blood pressure (BP) is detected. Using a Del Mar Avionics Recorder, ambulatory BPs were recorded automatically every 30 mins. for 24 hours in 12 stable male HD pts., aged 47.1 ± 11.1 yrs., and in 14 normotensive controls (C), aged 42.5 ± 10.3 yrs. At the time of study all 12 pts. were considered normotensive (9 without and 3 with antihypertensive drugs). Minimum (min) and maximum (max) systolic (S) and diastolic (D) BPs and heart rates were determined. In HD pts. 17.1% of DBP readings were 90-119 mmHg, only 8.6% were 90 mmHg or greater in C ($p<.01$). In HD pts. 30.7% of SBP readings were 140 mmHg or higher, 2.8% in C ($p<.01$). Max SBP was 155.3 ± 29.0 mmHg in C ($p<.02$); min SBP was 101.8 ± 15.0 mmHg in HD pts., 90.4 ± 9.2 mmHg in C ($p<.05$). Normotensive HD pts. had no significant difference in max or min DBPs and pressure-rate-products (PRP) were not significantly different in the 2 groups. Min PRP was higher in HD than C ($p<.01$). Analysis of BP readings obtained by 24 monitoring demonstated a higher frequency of BP elevations in HD pts. than C (a finding not revealed by casual readings). These results may indicate the need for initiating or increasing therapy in pts. who were considered normotensive.

SERIAL HEPATITIS B SEROLOGIC PROFILE OF A HEMODIALYSIS UNIT WITH ENDEMOEPIDEMIC HEPATITIS B. T.J. Kelly,* G.H. Mayor, M.J. Patterson.* Michigan State University, East Lansing, MI.

Some evidence of current or previous Hepatitis B infection can be found among the patients and staff of most chronic hemodialysis units. Reported here is an initial and 16 month follow-up survey of Hepatitis B serologic markers among patients of a unit with high endemic Hepatitis B. The three markers of Hepatitis B included in this survey were evaluated by commercial radioimmunoassays. The first survey included 35 patients: 4(11%) were positive for Hepatitis B surface antigen(HBsAg), 8(23%) had antibody to HBsAg(anti-HBs), and 18(51%) had detectable antibody to Hepatitis B core antigen (anti-HBc). Patients positive for HBsAg or anti-HBs all had concomitant anti-HBc while hepatitis exposure was evidenced only by anti-HBc in 6(17%) of the 35 patients. In total, 18 patients had at least one marker of Hepatitis B, a 51% prevalence. A follow-up survey conducted 16 months later revealed an increased prevalence of all markers among the 37 patients being treated at that time (18 patients participated in both surveys). In the follow-up survey, 9(24%) patients had HBsAg, 9(24%) were positive for anti-HBs, and 28(76%) had detectable anti-HBc. A total of 12(32%) patients were positive for "anti-HBc only" and at least one serologic marker was detected in 30(81%) of the follow-up patient group. Among the 18 patients included in both surveys, 10 had been negative for all three markers during the first survey. Among these ten patients on follow-up, one had only HBsAg, six had only anti-HBc, one had both HBsAg and anti-HBc, and two had developed no markers. These data illustrate the range of serologic response exibited among dialysis patients exposed to epidemic Hepatitis B.

PREVALENCE OF SERUM ANTIBODIES TO LEGIONELLA PNEUMOPHILA AND PITTSBURGH PNEUMONIA AGENT IN HEMODIALYSIS PATIENTS. Sheila Moriber Katz, Dept of Path, Joel Chinitz and Allan B. Schwartz, Dept of Med, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

Legionella pneumophila (LP) and Pittsburgh Pneumonia Agent (PPA) are recently identified bacteria that produce pneumonia in debilitated patients. Therefore, we studied prevalence of serum antibodies to LP (serogroups I - IV) and to PPA in 231 adult patients undergoing maintainance hemodialysis. One serum sample, obtained from each patient, was tested by the conventional indirect immunofluorescence test for antibodies to either LP or PPA, using appropriate positive and negative controls. Only 1 of 231 patients (0.4%) had a titer of $\geq$ 1:256 to LP, the level presumptive of past infection by LP. In that patient the titer was 1:512 to LP. Two other patients had titers of 1:64 to LP. Of the three patient with titers $\geq$ 1:64 to LP none had prior history of pneumonia. In addition, none of the 231 patients had a titer $\geq$ 1:64 to PPA. The prevalence of serum antibodies to LP in our population does not exceed that of middle age and elderly healthy persons (Storch, et al, J Inf Dis, 140:784-788, 1979). Therefore, our data indicates that patients on maintainance hemodialysis are not prone to develop infection by either LP or PPA.

THE METABOLIC AND ELECTROLYTE CHANGES SEEN WITH MIXTURES OF ACETATE AND SUCCINATE: POSSIBLE SOURCE OF FIXED BASE IN DIALYSIS. Paul L. Kirkendol, Carlos J. Devia*, David L. Schneider*, Maximo B. LaMarche, and Francisco M. Gonzalez. Depts of Pharmacology and Medicine, LSU Medical Center, New Orleans, LA.

The purpose of the present study was to determine the effects on plasma pH and electrolytes by mixtures of acetate (AC) and succinate (SUC) in acutely nephrectomized dogs. The mixtures used were 75% AC and 25% SUC, 50-50 mixture and 25% AC and 75% SUC. The mixtures were infused at a rate of 0.25 mEq/kg/min for one hour calculated as mEq of sodium. Blood samples were taken every twenty minutes for the first two hours and every hour for the next two hours. pH, hematocrit, Na^+, K^+, Cl^- and HCO_3^- were determined. The effects of these mixtures on HCO_3^- levels show that the 25% AC - 75% SUC mixture is similar to 100% SUC and the 75% AC - 25% SUC is similar to 100% AC. The 50-50 mixture seems to offer an advantage of rapid but less marked and more sustained production of HCO_3^-. The effects on pH are similar to those seen with HCO_3^- levels. All mixtures produced similar increases in plasma Na^+. None of the mixtures given had little effect on hematocrits of the animals tested. The mixtures used produced no marked changes in K^+ levels whereas AC alone decreased K^+ and SUC alone increased K^+ levels. All three mixtures produced decreases in plasma Cl^- levels similar to those reported for AC and SUC alone. Mixture of AC and SUC offer an advantage in changes in pH, HCO_3^- and K^+ levels when compared to each substance alone and a 50-50 mixture seems to be best combination to use as a source of fixed base.

NON-A NON-B HEPATITIS (NNH) IN HEMODIALYSIS PATIENTS: CLINICAL APPEARANCE ASSOCIATED WITH SERUM VIRUS AND A RELATED ANTIGEN (Ag) SYSTEM. AS Kliger, AE Williams*, MJ Bia, P Yap*, JD Wright*, AC Steere* and DJ Miller*. Yale University, New Haven, Ct.

Monthly SGOT and SGPT levels were measured in 46 hemodialysis patients (pts). Thirty-two pts had at least 1 elevated transaminase level, and 10 had 2 or more SGOT values > twice normal. Of these 10 pts 4 had symptomatic hepatitis (jaundice, anorexia or fatigue) and 6 were asymptomatic. The diagnosis of NNH was made when criteria for hepatitis A,B, and CMV were absent, and ethanol, hepatotoxins, and other causes of liver disease were excluded. The range of peak transaminase and bilirubin level was:

PATIENTS	SGOT	SGPT	BILIRUBIN
4 symptomatic	175-485	99-780	0.5-5.4
6 asymptomatic	110-210	82-740	0.5-2.8

One to 3 years before developing hepatitis, 6 of these 10 pts had intermittently elevated SGOT levels < twice normal. Sera from 7 of these 10 pts were examined by immunodiffusion for evidence of an Ag (RJ) and homologous antibody (Ab) recently described in pts with NNH. Five showed Ag to Ab seroconversion. Of the 32 pts with at least 1 abnormal transaminase, 16 of 22 that were tested for anti-RJ Ab were positive (73%), an incidence substantially higher than the prevalence of RJ Ab in unselected blood donors (21%). Sera of 6 pts with RJ Ag were examined by electron microscopy, and 4 showed the presence of spherical virus particles 80-120 nm in diameter with spike-like projections.

We have observed an outbreak of NNH characterized by minimal transaminase elevations in some pts. It is possible that the newly described RJ Ag and associated virus may play a role in the etiology of this disease.

MASSIVE PLEURAL EFFUSION SECONDARY TO CAPD. Edward Kuehnel, M.D. Providence & Portland Adventist Med. Centers, Portland, Oregon

A 58-year-old woman with analgesic-associated nephropathy had been on hemodialysis for 13 mos. when she underwent placement of a Tenckhoff catheter for CAPD. The CAPD involved 4 daily exchanges of 2L dialysate containing 1.5% dextrose. After 2 wks. of CAPD, chest x-ray showed small bilateral pleural effusions. After 3 wks. of CAPD with the patient normotensive and free of edema or fever, cough and right-sided pleurisy led to the diagnosis of a right-sided pleural effusion. Thoracentesis yielded 3500 cc of clear, yellow-tinged fluid - including 22 white cells/ML with a differential of 2% PMS, 70% lymphs, and 28% monos. The s.g. was 1.006 and the glucose 195 mg/DL. No organisms were seen on gram stain and none grew on culture. Post-thoracentesis film showed almost complete clearing of the effusion. One wk. later similar symptoms led to the discovery again of a massive pleural effusion. Repeat thoracentesis yielded 4,000 cc of fluid with similar laboratory studies. Again, post thoracentesis film was clear. Two days later the massive effusion had recurred. CAPD was discontinued and the patient returned to hemodialysis twice a week. A cannulogram done through Tenckhoff catheter, which was left in place, showed no leak of fluid from the peritoneal cavity into either pleural space. The pleural effusion cleared spontaneously over 3 wks. Both sides of the chest have remained clear since then. It is concluded that CAPD even when properly performed with good catheter position, may result in massive pleural effusion - which may limit the usefulness of this technique in certain patients.

● AMINO ACID LOSSES DURING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD). J. D. Kopple, M. J. Blumenkrantz, M. R. Jones*, J. K. Moran*, and J. W. Coburn, VA Wadsworth Med Ctr & UCLA Sch Med & Pub Hlth, Los Angeles, California

Although CAPD has been shown to have many therapeutic benefits, there is concern as to whether protein and amino acid (AA) losses may cause protein depletion. In the absence of peritonitis, dialysis protein losses were reported to be 4 to 15g/24 hr. However, there are virtually no data on losses of free AA during CAPD. Plasma and dialysate AA were therefore measured in 12 studies in 7 men undergoing CAPD, 3-5 exchanges/day, while they ingested either 78±6.7 SD (n=6) or 114±4.1 (n=6) g/protein day for 14 to 33 days during metabolic balance studies. Total AA losses did not differ with the two diets and averaged 3015±1591 mg/day with the lower protein diet and 3520±1092 mg/day with the higher protein intake. Of the total AA removed, 30±6% were essential AA. The dialysate AA concentrations averaged 74±16% of fasting plasma AA, and dialysate AA losses correlated with the daily volume of dialysate outflow ($r=0.65$, $p<.05$). The AA nitrogen (N) comprised 5.3±2.1 and 3.6±1.0% (NS) of total N output and 12±3.4% and 10±3.4% (NS) of non-urea N losses with the low and high protein intake, respectively. Fasting total AA were higher in CAPD patients than in 25 normal subjects (3187±741 vs. 2253±390 μmoles/L, $p<.01$). Thus the AA losses during CAPD do not reduce the AA levels and probably will not contribute to protein depletion. The high protein intake, relatively low AA losses, and absorption of glucose from dialysate may contribute to the good nutritional status seen in many of these patients.

● **PHARMACOKINETICS OF VANCOMYCIN IN CHRONIC RENAL FAILURE. F. Y. Lam*, A. Lindner, J. Plorde*, A. Blair* and R. E. Cutler. Seattle VA Medical Center**

The elimination rate of Vancomycin in end-stage renal disease (ESRD) on maintenance hemodialysis is reduced. However, few studies have attempted to measure pharmacokinetic parameters other than the half-life. In this study we measured several pharmacokinetic parameters in 7 patients with ESRD receiving chronic hemodialysis. Each volunteer received 1.0 gm of vancomycin in 250 ml of 5% dextrose in water intravenously over 45-60 minutes prior to a surgical procedure. Multiple plasma samples were obtained at 10, 20, 30, 45, 60 minutes and 2, 3, 4, 6, 12 hours; then daily for 10 to 14 days following the dose. Vancomycin was measured in plasma by a standard microbiological assay using Bacillus subtilis. The mean pharmacokinetic parameters (± SD) were: peak plasma concentration, 36.7 ± 7.8 mg/L; plasma clearance 5.6 ± 2.3 ml/min; elimination half-life 129 ± 38 hrs; steady state volume of distribution, 0.80 ± 0.11 L/Kg. The mean trough level at the end of one week was 6.6 mg/L, which is still within the therapeutic range. Using these results, computer simulation analysis showed that a schedule of 0.5 to 1.0 gm of vancomycin per week for 7 weeks in ESRD on chronic dialysis will reach a steady plasma level at peak of 24.1 to 48.2 mg/L and trough of 5.7 to 10.5 mg/L respectively. These levels are 3 to 5 times the minimal inhibitory concentration (2-3 mg/L) for 90% of S. aureus and would therefore provide adequate coverage for most infections by these organisms.

SEX, WORK STATUS, AND SURVIVAL IN LONG TERM DIALYSIS. Daniel E. Leb, Carol Stauffer,* Bonnie Freed‡ and Ellen Frank.* University of Pittsburgh, and Presbyterian-University Hospital, Pittsburgh, PA.

From January, 1968 through June, 1975, 234 patients with renal failure entered hemodialysis: 116 successfully trained for home dialysis (H), 126 had in-center dialysis (C), 114 received one or more kidney transplants (T). The distribution of patients surviving 5 years or more is:

	C	H	T
Alive	11	31	46
Dead	47	50	49

$Chi^2 = 13.35$ $p < 0.005$

Sixty-seven of 106 patients on dialysis in August, 1979 responded to a rehabilitation survey. Fully employed persons and homemakers whose activities were unimpaired were considered fully work rehabilitated. The responses tabulated by site of dialysis showed:

	Home	Center
Full Work	26	3
Not Full Work	24	14

$Chi^2 = 13.35$ $p < 0.025$

Of 27 married persons responding to a sexual satisfaction survey, only 4 of 22 home dialysis patients (18%) reported less satisfactory sexual activity. Two of 5 in-center patients (40%) were less satisfied. Satisfaction was estimated from the respondent's statement of satisfaction, frequency of intercourse, and number of problems. Compared to reports of similar studies on in-center patients, home dialysis patients appeared more sexually satisfied.

Home dialysis offers statistically better opportunity for survival and rehabilitation. Quality of life measured by sexual satisfaction is superior for patients on home dialysis.

LONGITUDINAL COMPARISON OF CHRONIC INTERMITTENT (IPD) AND CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD). Michael A. Madden,* Stephen W. Zimmerman, and David P. Simpson, (intr. by Stuart J. Updike). Dept. of Medicine, Univ. of Wisc., Madison, Wisc.

Twelve patients who received IPD for at least 3 months (mean 18.3), were switched to CAPD for at least another 2 months (mean 9.8), affording us opportunity to compare IPD versus CAPD in the same patient. Ten patients were male, 2 female, and the mean age was 55.4 years.

For almost all patients there was a decrease in mean BUN, S_{Cr}, uric acid, phosphorus (P), and K^+, comparing values drawn on CAPD with predialysis IPD values. Hematocrits (HCTS) significantly increased in 9 patients. Mean HCT after 6 months of IPD was 23±2%, and 32±1.9% after 6 months of CAPD. Despite some weight gain on IPD, weight on CAPD continued to increase, with a mean weight gain of 20±7.6 lbs at 10 months. BP was slightly lower on CAPD. 3 patients required BP medication on IPD. On CAPD, BP medication was stopped in one, decreased in one, and unchanged in the third pt. Serum albumin remained stable at about 3.6 gm/dl, and did not decrease on CAPD. Patients were usually able to decrease P-binders. Despite an increased incidence of peritonitis (1 episode/5.9 pt mo) on CAPD, vs IPD (1 episode/12 pt mo), there was less hospitalization (1.44d/pt mo) on CAPD compared to IPD (2.09 d/pt mo). Pt preference was for CAPD over IPD in almost all cases.

These results suggest that CAPD is adequate therapy for chronic uremia, and may have some advantages over IPD as reflected in higher HCTS, and better control of BP and P. Although the peritonitis rate doubled on CAPD, the requirement for hospitalization actually dropped due to ambulatory therapy of most of these infections.

COMPLICATIONS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD). Neil Lyman*, Kathleen Pierce*, Patricia Hanshaw*, Lawrence Byrd, Michael Gutkin, Ronald Viscuso*, and Martin Jacobs. Saint Barnabas Medical Center, Livingston, N.J., and College of Medicine & Dentistry, Newark, N.J.

We have reviewed our experience with 28 patients (pts) on CAPD for 336 pt weeks. After one year 61% (17) remained stable on this modality. Of those who were changed to another form of therapy, 67% (7 of 11) had polycystic kidney disease (PKD), and could not tolerate CAPD due to: change in body image by peritoneal fluid (2), recurrent peritonitis (2), respiratory insufficiency (1), catheter failure (1), and lower extremity (LE) gangrene (1). Since vascular insufficiency of the LE has previously been reported in CAPD pts, a study using pulse volume recordings of LE arterial blood flow and pressure was conducted. No significant changes were noted in pts erect with 2L of peritoneal fluid. Using the titanium adapter, monthly tube changes by the staff and plastic dialysate bags, 27 episodes of peritonitis occurred in 14/28 pts. However, 4 pts had 51% (14) of all peritoneal infections and these occurred early in their course. Organisms involved included Staph epidermidis (10), Strep species (4), Pseudomonas (4), Staph aureus (3), E. coli (2), Enterobacter (2), Flavobacterium (1), Bordetella bronchiseptica (1). The latter organism dwells in dog bronchi and was seen in a pt with a pet dog. Fungal and sterile peritonitis were distinctly absent. Conclusions: 1. PKD is a relative contraindication to CAPD. 2. Pulse volume recordings do not reveal hemodynamic changes of the LE in pts on CAPD. 3. Recurrent peritonitis occurs in a small subset of pts who can be identified early.

ZINC DEFICIENCY IN UREMIA. **S.K. Mahajan, A.S. Prasad,* P. Rabbani,* W.A. Briggs, and F.D. McDonald. V.A. Medical Center, Allen Park, Wayne State Univ., Detroit, MI.**

We have recently reported biochemical indicators of zinc (Zn) deficiency including low Zn in plasma, leucocyte (W.B.C.) and hair as well as increased serum ammonia and plasma RNA-ase in uremic patients. To document that uremia is a Zn deficient state, a double blind study using Zn acetate or placebo orally was initiated and their effect on these biochemical indicators was determined. Twenty four stable hemodialysis patients completed the study. Each had plasma Zn, WBC Zn, serum ammonia and plasma RNA-ase measured before and at intervals exceeding 6 weeks following therapy. Mean ± S.D., B=baseline, S=after supplementation, *p <.005 from baseline.

	Controls (N=10)	Treatment (N=12)		Placebo (N=12)	
		B	S	B	S
Plasma Zn (µg/100ml)	112±13	80±9	110±14*	81±10	82±7
W.B.C. Zn (µg/10^{10}cells)	107±19	56±13	109±18*	52±12	49±9
Ammonia (µg/100ml)	45±4	70±10	40±6*	68±11	64±7
RNA-ase (ΔOD/mm/ml)	0.4± .09	1.5± .06	0.8± 0.1	1.4± .08	1.3± .02

Plasma Zn and WBC Zn increased and serum ammonia and plasma RNA-ase decreased significantly in all patients on oral zinc therapy but not in those taking placebo. The results of this study suggest that uremia is a Zn deficient state and can be reversed by oral Zn supplementation. The mechanism(s) underlying Zn deficiency in uremia needs to be determined.

HEMODIALYZABILITY OF CYCLOPHOSPHAMIDE. Thomas C. Marbury, Lo-Hwa Wang,* Ching S. Lee,* and Bonnie L. Majeske. Univ. of Florida, Dept. of Nephrology & Pharmaceutics, Gainesville, Florida.

The hemodialyzability of cyclophosphamide was investigated prospectively in 4 chronic hemodialysis patients. Cyclophosphamide 100mg was given i.v. over 10 minutes prior to hemodialysis. Blood and dialysate samples were collected periodically during the 4 hour dialysis and measured by GLC for cyclophosphamide. Dialysis clearance calculated by arterial-venous difference and actual drug recovery in dialysate averaged 104ml/min. which compares favorably to the drug's metabolic clearance of 95ml/min. The extraction efficiency of the hollow-fiber dialyzers averaged 40% for both plasma and RBC samples. A mean of 37% of the administered dose of cyclophosphamide was removed during hemodialysis. The beta-phase showed a half-life of 3.3 hr. in our patients during hemodialysis which is a 49% reduction when compared to the 6.5 hr. half-life reported in uremic patients. Because of the significant reduction in eliminating half-life, large dialysis clearance compared to metabolic clearance, high extraction efficiency, and significant drug removal during dialysis, we conclude that cyclophosphamide is dialysable.

LIPOPROTEIN LIPASE INHIBITOR REMOVAL DURING HEMOFILTRATION OF RENAL FAILURE PATIENTS. Alisa Minear Eiji Minami, James Blankenship and Stewart Shankel* Loma Linda Univ. & Jerry L. Pettis Memorial VA Hospital, Loma Linda, CA.

The present study was undertaken to determine whether or not an inhibitor of lipoprotein lipase can be removed from uremic plasma by a large pore size dializer.

Hemofiltration, a relatively new technique for removing greater quantities of fluids and larger toxic substances from uremic plasma than conventional hemodialysis, has been shown to effect a decrease in triglycerides in hypertriglyceridemic renal failure patients by some unknown mechanism.

Plasma from seven hypertriglyceridemic (> 150 mg/100ml) chronic renal failure patients was found to inhibit triglyceride lipolysis by lipoprotein lipase purified from bovine skim milk. Activity of the enzyme as measured by radiolabelled free fatty acid release was reduced 8 to 67% by uremic plasma in comparison to a control plasma from a subject with triglycerides in the normal range (44 mg/100 ml). Ultrafiltrate removed during the process of hemofiltration, by a large pore size hollow fiber dializer, Amicon Diafilter ^{TM}30, was found to inhibit lipoprotein lipase activity from 22 to 66% (Ave. 42%), in contrast to dialysis fluid taken off during regular hemodialysis with a Cordis Dow hollow fiber 1.8 dializer, which had enzyme activating properties (Ave. 21%).

It is proposed that the triglyceride-lowing effect observed subsequent to hemofiltration treatments is a result of the removal of one or more inhibitors of lipoprotein lipase from the plasma of hypertriglyceridemic renal failure patients.

MYOCARDIAL PERFORMANCE DURING DIALYSIS WITH DIALYSATE CONTAINING ACETATE, HCO_3 AND SEQUENTIAL ULTRAFILTRATION AND DIALYSIS. Jovan Milutinovic, Soad Bekheit, Leroy Lapp; West Virginia University, Morgantown, West Virginia.

The effect of hemodialysis (D) with dialysate containing acetate (AD), bicarbonate (BD) and sequential ultrafiltration and AD (UAD) on arterial blood gases (ABG) and cardiac performance (CP) was assessed in 10 patients (pts) divided into: Group I (4 pts) and Group II (6 pts) without and with cardiac failure (CF), respectively. Paired studies were made for each D in each pt. Systolic time ratios (PEP/LVET), mean blood pressures (MBP), heart rates (HR), ABG's and pH were measured before and at hourly intervals during D which lasted 4 hours. Left ventricular dimensions (LVD),ejection fractions (EF) and fibre shortenings (VCF) were measured from M-mode echocardiography before and after D.

Changes in Measurements at 4th h of Different D

	gp I			gp II		
	AD	BD	UAD	AD	BD	UAD
HR/M	+11	+10	+8	+11*	+13*	+10
MBP mmHg	-17*	-4	-11	-19*	-9	-18*
PaO_2	-10	-2	-9*	-16*	-11	-10
$PaCO_2$	-3.1	-0.8	-1.2	-2.6	-2.3	-3.9
pH	+0.1*	+0.1*	+0.06*	+0.05*	+0.11*	+0.08*
PEP	+0.09	+0.05	+0.14	+0.18**	+0.11	+0.16*
LVET	**P<0.001			*P<0.01		

Changes in LVD, EF, and VCF were insignificant after all D. Increase in PEP/LVET, decrease in PaO_2 and MBP were greater with AD, particularly in pts. with CF.

Because of increased incidence of cardiac dysfunction with AD, it should be avoided particularly in pts. with CF.

ACUTE FLUORIDE INTOXICATION IN HEMODIALYSIS PATIENTS. *G. Mitchell*, W. Cirksena, G. Samaras*, C. Wax*, Biomedical Applications of Annapolis, Annapolis, MD.*

Eight patients with end stage renal disease while undergoing hemodialysis were exposed to softened tap water which had been accidently contaminated with hydrofluosilicic acid, raising the fluoride concentration to approximately 50 times normal. Hours prior to dialysis, 1000 gallons of hydrofluosilicic acid had been spilled into the public water supply of the city of Annapolis, MD, and had gone unreported. All 8 patients developed a gastrointestinal illness of varying severity. One patient experienced cardiac arrest and one died suddenly with high tissue fluoride levels at autopsy. Four patients had elevated LDH and CPK of skeletal muscle origin. Samples of urine and sera as well as dialysate and tap water had markedly elevated fluoride levels. At the time of the fluoride accident there was no system at the dialysis unit to remove anions from the incoming municipal water. As there are no current Federal regulations specifying methods of water purification in chronic units, the potential for similar accidents remains in municipalities that fluorinate their water. We feel that standards should be developed for dialysis water treatment which consider both advantages and disadvantages of dialysis purification systems.

REVERSIBLE ALTERATION IN PERITONEAL PERMEABILITY BY CYTOCHALASINS IN RATS. *B.K. Mookerjee, N. Alavi,* E. Lianos,* J. Van Liew and C. Bentzel. VA Medical Center and SUNY/Buffalo, Buffalo, N.Y.*

Cytochalasins (Cy) are fungal metabolites that disrupt microfilaments and alter tight junctional permeability in the Necturus gallbladder. Effects of Cy B, D and E were studied during peritoneal dialysis by maintaining constant plasma levels of urea (small molecular probe) and ^{3}H-inulin (intermediate probe), while proteins (albumin and proteins of large and small molecular wts) were measured by gradient microelectrophoresis in polyacrylamide gel. In cycles 1-3 (control) Ringers lactate (RL) was instilled. Cy B (3-10 μM) was incorporated into RL in cycles 4-7 while during recovery (cycles 8-11), RL only was used. Permeability (P) was calculated graphically for each cycle by plotting Cd·V/(Cp-Cd) vs time (15 min cycle) where Cp and Cd are concentrations of ^{3}H-inulin and urea in plasma and dialysate, respectively and V=dialysate volume (30 ml). Cy B increased P to inulin and urea by 74% and 45%, respectively while total peritoneal protein concentration increased 60% (n=8). Change in protein permeability was non-selective. Obliteration of mesothelial microvilli (scanning EM), focal aggregation of submembranous microfilaments (transmission EM) and intact paracellular tight junctions (freeze fracture EM) was observed. P to urea and proteins returned towards normal values during recovery. Conclusions: (a) Cytochalasins increase peritoneal permeability to small, intermediate and large molecules without altering structure of tight junctions. (b) Effects may be due to change in cell membrane permeability and/or area; (c) Cy D and E are 5-10 fold more potent than Cy B on a molar basis.

CHRONIC AMBULATORY PERITONEAL DIALYSIS(CAPD) IN HIGH RISK PATIENTS WITH RENAL FAILURE: MORBIDITY AND MORTALITY. P.J. Olsson,* F. Horvath,* R. Bingham,* R.L. Carter,* J.C. Peterson,* and D.R. Mars. Univ. of Fla., Gainesville, FL.

The efficacy, morbidity, and mortality of CAPD was compared to hemodialysis (HD) in high risk patients using a retrospective matched pair analysis. All patients had juvenile or adult onset diabetes mellitus or were greater than 70 years of age and had severe diabetic vascular disease, congestive heart failure, massive obesity, or class IV angina. Most of the diabetic patients were blind in at least one eye. Statistically, there was no difference in BUN, creatinine, Ca, P, glucose, or serum albumin in the two groups. However, control of blood pressure and anemia was better in CAPD patients. Average hospitalization time during the period of study was significantly less in CAPD patients (18.6 days vs 41.6 days, $p<0.05$). Three deaths occurred in the HD group, none in the CAPD group.

Our data suggest that in comparison with HD, CAPD is equal to or superior to HD in the management of endstage renal disease in high risk patients. In addition, because of reduced hospitalization and the lower intrinsic cost of the dialysis procedure, CAPD is a more cost effective form of treatment in this group of seriously ill high risk patients.

COMPARISON OF CONVECTIVE AND DIFFUSIVE SOLUTE REMOVAL DURING CLINICAL AND SIMULATED PERITONEAL DIALYSIS. K. Nolph, M. Sorkin, T. McGary,* H. Moore,* Department of Medicine, VA Hospital and University of Missouri, Columbia, Missouri

In peritoneal dialysis, low clearances of urea and creatinine may be due to fluid films in the peritoneal cavity. Net sieving of Na and K during osmotic ultrafiltration (UF, ml/ex) could be due to molecular interaction with glucose within the membrane rather than to membrane properties per se. In vitro simulations (21 two liter exchanges (ex)) of peritoneal dialysis with cellulosic fibers as capillaries were carried out. For Na and K, dialysate/perfusate concentration ratios (D/P), convective mass transfers (CMT, mEq/ex) and net sieving coefficients at high UF (SC=CMT/UF/P) were compared to results in 37 clinical 2L exchanges. Urea and creatinine solute equilibration curves were compared. At cycle times of 240 minutes with physiologic blood path concentrations of Na and K, and dialysate Na and K at 132 and 0 mEq/L, mean results of 1.5% and 4.25% dextrose exs respectively were:

	Glucose	UF	Na D/P	K D/P	Na CMT	K CMT	Na SC	K SC
In Vivo	1.5%	313	0.95	0.83	21	0	--	--
	4.25%	533	0.95	0.88	61	1.0	0.77	0.46
In Vitro	1.5%	160	1.0	0.98	21	0.2	--	--
	4.25%	330	1.0	0.99	38	1.1	1.0	1.0

Equilibration curves (1.5%) showed D/P urea and D/P Cr increasing identically in simulated studies and nearing 1.0 at 200 min. In humans D/P urea was 0.75 and D/P Cr 0.66 at 200 min. Summary: Relatively low CMT/UF and slow equilibration across the human peritoneum must relate to endothelial, mesothelial, and/or interstitial resistances (not only cavitary fluid films or simple physical-chemical effect of glucose).

EFFECT OF PROSTACYCLIN (PGI_2) ON UREA CLEARANCE (U_{cl}) IN CONSCIOUS DOG. R.V. Patak, T.B. Wiegmann,* and D.A. Diederich*. Univ. of Kansas Medical Center and V.A. Medical Ctr., Kansas City, Mo.

We compared the effects of a potent platelet aggregating inhibitor PGI_2 (Group I, N=3) with standard anticoagulant - heparin (Group II, N=3) on U_{cl} in dogs. Hemodialysis was done by cannulation of femoral artery to vein with a hollow fiber kidney (THF 1500). Dialyzer blood flow (Qb) rates were varied between 50 to 140 ml/min by a calibrated pump at 30 minute intervals. 2.5 M. urea in 10% invert sugar was infused to maintain an arterial urea concentration of 63±2 mM/L. Group I received 1000 IU heparin at the set-up of the dialyzer followed by a constant infusion of PGI_2 (2 μgm/min). Group II received 3500 IU heparin bolus followed by a constant infusion to keep clotting time above 60 minutes. U_{cl} was measured after each time interval. Results (mean ± SE):

Ave.Qb. ml/min	50	75	100	140
Group I (PGI_2)	50±.3	68±1.6	98±.7	128±5
Group II (heparin)	44±.3	62±.7	87±.7	105±2.0

Group I had significantly higher U_{cl} ($p<.05$) at every Qb when compared with Group II. Furthermore, Qb dependent increase in U_{cl} remained linear throughout the experiment in Group I and showed an exponential decline above 100 ml/min in Group II. We conclude: PGI_2 enhances U_{cl} in dogs. These studies further suggest that PGI_2 may minimize or effectively replace the use of heparin in hemodialysis. Further studies are needed to assess the use of PGI_2 in high risk patients with bleeding tendency after heparin administration.

HEMODIALYSIS ASCITES IN ANEPHRIC PATIENTS.
S. Popli, W.T. Chen, S. Nakamoto, J.T. Daugirdas*, L.E. Cespedes, and T.S. Ing. Cleveland Clinic, Cleveland, Ohio and Veterans Administration Hospital, Hines, Illinois.

Bilateral nephrectomy has been reported to improve ascites, refractory hypertension, and cachexia in certain maintenance hemodialysis patients. To the contrary, we encountered 6 adult maintenance hemodialysis patients in whom ascites first developed (4 cases) or recurred (2 cases) after bilateral nephrectomy. In each patient, diagnosis of hemodialysis ascites was established by exclusion, after a careful evaluation had failed to reveal other possible causes for ascites. Peritoneal fluid protein concentration was typically elevated in each case.

In two patients, successful renal transplantation was accompanied by resolution of ascites. In the remaining patients, ascites persisted despite vigorous ultrafiltration during hemodialysis.

The course of these patients suggests that the presence of the kidneys is not required for hemodialysis ascites to occur. Use of nephrectomy to treat this form of ascites should be re-evaluated.

CORRECTION OF HYPOTENSION EARLY IN DIALYSIS BY SUBSTITUTION OF ACETATE WITH BICARBONATE.
G.A. Posen and R. Mikhael*, Ottawa Civic Hospital, University of Ottawa, Ottawa, Canada.

Hypotension within the first half hour of dialysis was observed to be a problem with a select group of our patients (pts). A study was conducted to investigate the role of acetate in the dialysate in precipitating this problem and to attempt its prevention with the use of bicarbonate, administered intravenously or as a substitute for acetate. The 6 pts studied were all elderly (>65) and had histories of heart disease. Eight stable dialysis pts served as controls. BP, body wt, S.Osm, temp, hb, hct, electrolytes, S.acetate and astrup were measured initially, at time of BP fall and when BP stabilized; in controls, initially after 40 min and again after 60 min from start of dialysis. These studies were repeated in 15 dialyses, when hypotensives were given 50 mEq Na bicarb intravenously 5 min after onset of dialysis and again in 29 dialyses, with the substitution of Na bicarb for acetate in the dialysate. In the hypotensive pts there was no change in body wt, SOsm, hb, hct, or temp at time of BP fall. Comparing the hypotensive and control group there was no significant differences between the astrup, S.acetate levels or electrolytes initially, at 40 or at 60 min. The use of IV bicarb corrected the initial pH status of the hypotensive group but did not prevent the BP fall. Substitution of bicarb for acetate in the dialysate did prevent hypotension in all 6 pts. This small group of elderly pts with damaged hearts were sensitive to the cardiodepressive actions of acetate. Early hypotension was prevented in these pts by substituting bicarb for acetate in the dialysate not by correcting acid base abnormality.

TREATMENT OF UREMIC PERICARDIAL EFFUSION BY LOCAL STEROID INSTILLATION VIA SUBXIPHOID PERICARDIOTOMY.
S. Popli, T.S. Ing, J.T. Daugirdas*, E.O. Osanloo, R.M. Vilbar, and R. Pifarre*. Veterans Administration Hospital, Hines, Illinois.

Intractable pericardial effusion is commonly encountered among maintenance hemodialysis patients. Successful treatment of this condition has been recently reported by instillation of a non-absorbable steroid into the pericardial sac via a percutaneously placed indwelling catheter. Due to the potential hazards of that blind procedure, we used a differenct approach to treat 12 patients with intractable pericardial effusion. A wide-bore catheter was inserted under direct vision, using local anesthesia, into the pericardial space via subxiphoid pericardiotomy. After overt bacterial infection had been excluded, 50-100 mg of triamcinolone hexacetonide were instilled aseptically at 6-hour intervals. After each instillation, the tube was clamped for 2 hours and then left to closed drainage. Using this treatment, all effusions resolved within 48-120 hours. During a follow-up of 3-36 months, no recurrence of effusion was detected, and constricitive pericarditis was not encountered. Four patients did develop wound infections at the catheter skin exit site. These infections resolved without incident after treatment with parenteral and/or local antibiotics.

Our results suggest that insertion of a pericardial catheter via subxiphoid pericardiotomy for drainage and local steroid instillation is a safe and simple procedure for the treatment of intractable uremic pericardial effusion.

EFFECT OF SUBSTITUTION FLUID CALCIUM CONCENTRATION [Ca] ON PLASMA IONIZED CALCIUM [Ca++] AND PARATHYROID HORMONE [PTH] DURING HEMOFILTRATION [HF].
Wajeh Y. Qunibi*, Margaret S. Izzo*, Richard B. Freeman. Department of Medicine, University of Rochester Medical Center, Rochester, New York.

Plasma [Ca++] and PTH levels are important parameters in the pathogenesis of renal osteodystrophy. To study these parameters during HF, experiments were performed using an Amicon 40 hemofilter in post-dilution mode and varying substitution fluid [Ca] ie. 2.5, 3.0, 3.5, and 4.0 mEq/L. Each substitution fluid [Ca] was used in two successive experiments. We measured [Ca++] and PTH in plasma and filtrate before and after HF. [Ca++] was measured by Orion ion selective flow-through Ca electrode and PTH by RIA using rabbit anti-bovine PTH for C-terminal fragment.

The rise in plasma [Ca++] from pre to post-HF was significant only when substitution fluid [Ca] of 3.5 or 4.0 mEq/L was used ($p<0.005$). There was substantial removal of PTH in the filtrate. An inverse relationship between post-HF [Ca++] and PTH level prior to the next HF treatment was found ($r= -0.88$, $p<0.01$) and between post-HF [Ca++] and ΔPTH during the treatment-free interval ($r= -0.74$). Post-HF plasma phosphorous concentration was comparable in all experiments.

Conclusions: 1.) The use of high substitution fluid [Ca] of 3.5 or 4.0 mEq/L is necessary to increase the plasma [Ca++] during HF. 2.) During HF, using high substitution fluid [Ca], there was blunting in the rise of PTH before the next HF treatment. 3.) High substitution fluid [Ca] may be beneficial in controlling renal osteodystrophy.

DECREASED ULTRAFILTRATION (UF) IN CAPD PATIENTS DURING PERITONITIS-ROLE OF GLUCOSE TRANSPORT. R. Raja, M. Kramer, J.L. Rosenbaum, C. Bolisay* and M. Krug*. Renal Section, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

Some pts cannot continue CAPD due to inadequate UF. It was noted that CAPD pts retained excessive fluid with peritonitis. UF was 605±75 ml in pts without and 414±83 ($P < 0.05$) with peritonitis with 4.25% dialysate (D) for 8 hr exchanges. This study compares UF and solute transport in 6 pts at the beginning of CAPD (A), during peritonitis (B) and 72 hrs after peritonitis cleared (C) utilizing 4.25% dialysate with 2 hr and 8 hr exchanges. Urea (U), Cr, glucose (G), Na and Osm were determined in blood and dialysate. Clearance (K) for U and Cr from blood and G influx was calculated. The results are as follows: (Mean±SEM)

	K_U	K_{Cr}	K_G	UF	P/D Osm**
		ml/min		ml	
A	14±1	12±1	10±2	640±72	0.91
B	21±2*	20±2*	18±3*	405±86*	0.96*
C	15±2	12±1	11±3	620±63	0.90

* $P < 0.01$ ** End of exchange

The % increase was 50, 66 and 80 for K_U, K_{Cr} and K_G with peritonitis. For 8 hr 4.25% exchange P/D glucose was 0.3±0.1 without and 0.5±0.2 during peritonitis. K_G had indirect correlation with UF but direct with K_U and K_{Cr} during peritonitis ($P < 0.05$). These data suggest: 1) UF in CAPD pts may be decreased during peritonitis. 2) This may be due to lower osmolar gradient from enhanced glucose absorption and may be avoided by using non-absorbable osmotic agent. 3) The greater increase in % K_G than K_U and K_{Cr} with peritonitis may partially be due to bacterial glucose consumption.

●CHEMILUMINESCENCE (CL) AND SUPEROXIDE ANION PRODUCTION IN LEUKOCYTES (PMN) FROM CHRONIC HEMODIALYSIS (CHD) PATIENTS (PTS). E.E. Ritchey*, J.D. Wallin & S.V. Shah. Nephrol. Sect., VAH & Tulane Univ. Med. Ctr., New Orleans, Louisiana.

Infection is a significant cause of morbidity and mortality in CHD pts. To assess the oxidative burst (intimately involved in antimicrobial activity in PMN) we studied superoxide production and luminol-amplified CL in PMN from CHD pts and in age matched controls (Θ) in the resting state and in response to phorbol myristate acetate (PMA).

	Autologous Serum			Crossover Studies Ψ	
	Resting	Δ↑		Resting	Δ↑
Control	(20) 10±1¶	76±5	(15)	17±3†	79±9
CHD Pts	(17) 14±3	60±5§	(13)	8±1†	62±5

Ψ Control PMN in CHD Pts serum; CHD Pts PMN in control serum. ¶ All values represent peak cpm x 10^3/1 x 10^6 PMN ± SEM. § $p < 0.05$ compared to control. † $p < 0.05$ compared to autologous serum.

Studies after hemodialysis (n=9) showed significant reduction in resting CL values; however decreased response to PMA remained. No differences either in resting or PMA stimulated superoxide production were seen in PMN from CHD pts (n=24) compared to Θ (n=24). These results indicate: a) resting CL in PMN from CHD pts is higher due to dialyzable factor(s) in serum; b) CL response of PMN from CHD pts to PMA is decreased; this is not improved by normal serum or after dialysis; c) the decreased CL response is due to superoxide anion independent mechanisms. Since CL is a sensitive measure of oxidative metabolic potential of PMN and correlates well with antimicrobial activity, the reduced response to PMA observed in PMN from CHD pts may explain in part the increased susceptibility to infection in CHD pts.

ADVERSE OCULAR EFFECTS OF ACETATE HEMODIALYSIS. *B. Rever*, L. Fox*, Y. Bar-Khayim*, A. Nissenson, Div. of Nephrology, Dept. of Med. and Dept. of Ophth., UCLA Center for Health Sciences, Los Angeles, Ca.*

Increased intraocular pressure (IOP) reportedly occurs during the course of hemodialysis (HD). This has been attributed to an osmolality dysequilibrium between serum and posterior chamber during rapid HD To clarify this phenomenon more precisely we examined the ocular changes that occur with HD. 14 subjects were studied: 6 during acetate HD (HD-A), 4 during HCO_3^- HD (HD-B) and 4 normal controls (C) not on dialysis. Studies were performed during a 4-hour HD in the uremics and over a 4-hour period in the controls. IOP, anterior chamber depth (ACD), and serum osmolality were measured hourly. IOP was measured with an Alcon pneumotonometer and ACD with a Zeiss slit lamp with an ACD pachometer. Results are expressed as mean ± SE of all pre and post dialysis values.

		IOP (mmHg)	*p*	*ACD (mm)*	*p*	*OSM*	*p*
C	*pre*	*15.4±0.7*	*NS*	*3.75±0.33*	*NS*	*284±3*	*NS*
	post	*14.9±1.0*		*3.76±0.30*		*285±2*	
HD-A	*pre*	*16.2±0.6*	*NS*	*3.39±0.08*	*<.025*	*310±2*	*<.05*
	post	*16.4±0.9*		*3.28±0.09*		*295±5*	
HD-B	*pre*	*14.7±1.7*	*NS*	*3.16±0.18*	*NS*	*317±7*	*<.01*
	post	*16.1±1.6*		*3.16±0.53*		*298±9*	

Conclusions: 1) Contrary to previous reports HD-A and HD-B are not associated with an increase in IOP; 2) Significant narrowing of ACD occurs only in HD-A despite equivalent changes in serum osmolality in HD-A and HD-B; 3) HD-A should be avoided in patients with a history of glaucoma or recent eye surgery.

THE EFFECTS OF CHRONIC RENAL FAILURE (CRF) ON SERUM LEVELS OF HUMAN PANCREATIC POLYPEPTIDE (PP). RW Rosenbaum, J Prasad, P Hendricks,* G Mayor, and R Gingerich,* Michigan State University, East Lansing-Saginaw, MI and Washington University, St. Louis, MO.

The kidney is known to play a key role in the metabolism of many low molecular weight peptides. However, its contribution to PP metabolism is unclear. We, therefore, evaluated serum levels of PP in patients with CRF to determine this relationship. Following an overnight fast and prior to hemodialysis, serum PP levels were determined for 6 hours subsequent to the ingestion of a standard protein meal in 10 normal and 7 CRF subjects. Results are expressed as the mean±SEM pg/ml. Mean PP levels were approximately 10-20 fold greater in CRF subjects at all sampling times, including basal (NL=84±6, CRF=1834±439), and peak 15 minute (NL=349±52, CRF=4082±1238) levels. However, due to the marked variability seen in the range of values for CRF subjects (Basal=658-3633 pg/ml and Peak=1238-10,532 pg/ml) statistical significance was obscured. CRF subjects demonstrated a two fold increase in peak values as opposed to the 4-6 fold increase seen normally. Gel chromatography was performed on one CRF sample with the greatest absolute PP value. The elution profile demonstrated a single major peak of immunoreactivity migrating at the same position as purified porcine PP standard. This data suggests that the majority of the increased PP immunoreactivity measured in our CRF subjects represents intact hormone. On the basis of the markedly elevated, though variable, levels of PP found in CRF subjects, we conclude, that the kidney plays a significant role in the metabolism of PP.

VASCULAR ACCESS (VA) IN ACUTE RENAL FAILURE (ARF). Dale Rowett, Middlesex Hospital, Middletown, Ct.

To determine the feasibility of femoral vein cannulization for blood draw and peripheral vein cannulization for blood return in dialysis, 41 patients requiring 128 hemodialysis treatments were studied prospectively. Femoral vein cannulization was used where possible. Otherwise the subclavian or the internal jugular vein was cannulated, using the Uldall cannula. Where possible, blood return was established with a 14 gauge Deseret dialysis cannula in an antecubital vein.

Femoral vein cannulization was possible in 33 of 41 patients-80.5%. Reasons for failure were recent bilateral femoral artery surgery (4), iliofemoral thrombosis (2), massive carcinomatous inguinal lymphadenopathy (1), and unexplained (1). In these 8 patients, the subclavian vein (6) and internal jugular vein (2) were used. Antecubital vein blood return was possible in 31 of 41 patients-75.6%.

It is concluded that VA is possible in all patients with ARF without the use of arteriovenous shunts or single needle devices. Blood return via antecubital vein is possible in the majority of patients with ARF. Femoral vein cannulization is not possible in all patients with ARF. The dialysis physician should become experienced in cannulating the femoral, subclavian, and internal jugular veins.

PERITONEAL DIALYSIS DURING PERITONITIS. Jack Rubin, John Bower. Univ. of Miss. Med. Cntr., Jackson MS

We studied the effect of peritonitis during peritoneal dialysis upon protein losses in the dialysate, clearances, glucose absorption (Aglu) and effluent volume. Nine pts aged 44.4 ± 5.4, 22-70 yrs, underwent a series of exchanges (2L; in 10 min dwell 30 min, drain 20 min) When peritonitis was diagnosed (abdominal tenderness, elevated dialysate cell count, culture yielding organisms) pts underwent L exchanges, infusion and immediate drainage until the effluent was no longer turbid or symptoms were relieved. Study exchanges were then obtained. Antibiotics, K+, and heparin were added to dialysate as required. Blood was sampled bracketing the control exchanges and at the start of the rapid exchanges during peritonitis. There were 15 episodes of peritonitis in 9 pts (5 Gm(+), 8 Gm(-), 1 fungal, 1 no growth, median initial dialysate cell count 1965/mm^3, average time between studies 37 days). One mean value per pt for each parameter studied was obtained. The results are:

	Cur ml/min	Ccr ml/min	Aglu mg	Protein Loss/Ex	Efflu. Vol ml
Control	14.99 ±0.97	11.37 ±1.07	5368.3 ±585.5	1088.9 ±170.2	2219.7 ± 17.3
Peritonitis	18.15* ±1.05	16.7* ±1.01	9408.2* ±1066.4	1422.67* ±247.68	2128.7* ± 17.8

*P < .05 (paired-T test)

Peritonitis is associated with increased protein losses, peritoneal clearances, Aglu, and decreased effluent volume. These changes may be explained by alterations in peritoneal blood flow and/or permeability secondary to peritonitis.

FALL IN SERUM CREATININE IN MAINTENANCE HEMODIALYSIS PATIENTS AFTER CESSATION OF ANABOLIC STEROIDS. J.E. Rubin, M.V. Feinroth*, M. Feinroth*, E.A. Friedman, G.M. Berlyne, Renal Section Brooklyn VA Medical Center-Downstate Medical Center Brooklyn, N.Y.

Anabolic steroid administration is used to augment the hematocrit of maintenance dialysis patients. They also increase muscle mass which would thus increase creatinine levels. Anabolic steroid administration was suspended for a 3 month period to determine if creatinine levels would be affected. During this time the patients' diet dialyzers and time of dialysis were unchanged. The mean age of the 25 patients studied was 55.9 years, 12 were white and 13 were black. The sign test was used to evaluate data.

After the 3 month period mean serum creatinine fell to 15.8 mg/dl from 17.4 mg/dl ($p < .05$). Mean hematocrit fell to 24.5% from 27% ($p < .05$). There was no significant change in the mean value of blood urea nitrogen during this time.

It is concluded that anabolic steroids increase muscle mass and cause greater creatinine production with increased serum creatinine levels. This fact must be considered when using creatinine values as a measure of effective dialysis in patients receiving these agents.

● PROSTAGLANDIN E (PGE) BLOOD LEVELS DURING HEMODIALYSIS (HD): COMPARISON OF CELLULOSIC (CL) AND POLYACRYLONITRILE (PAN) MEMBRANES. G. Schmitt, M. Tobin*, J. Matheson* and W. Flamenbaum. Renal Section, Boston VA Medical Center, Boston, MA.

Recent work suggests that HD may induce hypotension. We investigated the effect of HD on the blood levels of PGE, a natural vasodilator. Blood samples were drawn pre-HD, and at frequent intervals during HD from the arterial (inflow) and "venous"(outflow) lines of the dialyzor. The studies compared a CL (n=8) with a PAN (n=4) membrane. Mean arterial (A) and veno-arterial (VA) PGE levels (pg/ml) were:

time		0"	5"	15"	30"	120"
CL:	A	292	640	606	658	246
	VA	-	100	414	332	207
PAN:	A	330	720	1039	521	164
	VA	-	8	-321	-16	23

None of the patients studied manifested a hypotensive episode. HD with either membrane is associated with an initial two- to three-fold rise in PGE levels. The CL membrane was associated with a positive VA difference, for the initial 30 min of HD. In contrast, the PAN membrane was not, suggesting the removal of PG, with or without diminished generation of PG by this membrane. Considering the molecular weight of PGE (354), this may be an intrinsic characteristic of HD with a PAN membrane. The potential role of PGE, or other vasoactive hormones, in the pathogenesis of HD associated hypotension remains to be clarified. Our results indicate, however, that one modulating factor may be related to the specific membrane (CL, or PAN) used for HD.

A MODIFIED MIDDLE MOLECULE HYPOTHESIS. F. H. SHEN* (intr. by F. Curtis), Univ of Wash, Seattle, WA.

The original middle molecule (MM) hypothesis which was based on a single compartment model defined the minimum adequate clearance as 3 ml/min (e.g. Dialysis Index = 1). This was regarded by many as low judging from clinical experience. The incorporation of KCr=8 ml/min in the latest version of MM hypothesis was one step closer towards reality but also killed the main spirit of the hypothesis itself. Since most molecules except urea behave as existing in a 2 compartment system, we attempt to revise the MM hypothesis by adopting Popovich's model (ASAIO 21:108, 1975). A clearance (Kd) and molecular weight (MW)-dependent efficiency ratio (ε) can be calculated for a 5 hr-dialysis with regular Gambro: 0.94, 0.86, 0.66, 0.80 and 1.00 respectively for urea, creatinine, sucrose, B_{12} and inulin. The "effective" clearance is defined as the product of conventional clearance and the ratio, (e.g. εKd). A εKd vs MW curve can be constructed for Gambro and a separate one for Kiil by using the original data for MM hypothesis (ASAIO 17:81, 1971). A similar curve can also be constructed for CAPD without such compartmental adjustment because ε approaches unity when Kd is below 20 ml/min. When these 3 curves are plotted together they intersect at a point indicating the size of the uremic toxin(s) is probably 380±50 daltons and the minimum adequate clearance is 5 ml/min. Furthermore this revised MM hypothesis also fits well with data obtained from IPD and hemofiltration. We conclude this modified MM hypothesis which recognizes the significance of transcellular transport resistance and thus scales down the size of the MM is by far the best model to provide a unified theoretical explanation for all the existing treatment modalities.

NITROSODIMETHYLAMINE (NDMA) IN DIALYSATE WATER AND BLOOD OF CHRONIC DIALYSIS PATIENTS (CDP). Michael Simenhoff, Stephen Dunn,* and Joseph Smiley, Dept. of Med., Thos. Jefferson Univ., Phila., PA.

We have shown dimethylamine, a precursor of a potent carcinogen NDMA in CDP. Because of reported increased incidence of cancer in CDP we assayed for volatile nitrosamines in extracts of dialysate water, following various standard purification treatments, and blood in CDP from 16 dialysis units using gas chromatography combined with a Thermal Energy Analyzer. Table I shows NDMA (ppb) found in dialysate water. Municipal water and dialysate electrolyte concentrates were free from NDMA. Table II shows NDMA (ppb) in blood of 10 patients (Group III) at 3 time intervals from 2 units where NDMA in dialysate water was highest. Control group represents blood levels of 11 patients from units where NDMA was very low (Group I). Results show NDMA is found in dialysate when certain water treatments are used.

TABLE I

Group		Range	Mean	SEM
I	11 units (n=20)	0-0.05	0.0025	0.0025
II	3 units (n=5)	0.20-1.8	0.62	0.30
III	2 units (n=25)	1.4-31.8	12.0	2.3

TABLE II

	Pre-dial.	15 min.dial.	Post-dial.
Control	0.02±0.01	0.07±0.04	0.08±0.04
III	0.10±0.02	1.9 ±0.97	0.57±0.26

Because of a chemical gradient, NDMA enters the blood as demonstrated by data obtained after 15 minutes of dialysis. Raised post dialysis NDMA level in Group III is less but still present. Water purification systems should be reviewed to eliminate generation of potentially harmful compounds.

SALIVA ZINC LEVELS AND TASTE ACUITY IN HEMODIALYSIS PATIENTS. A. Silverstein*, P. Fein, and M.M. Avram. Long Is. Coll. Hosp., Brooklyn, N.Y.

Taste loss in uremia is a serious clinical problem. Salivery zinc levels have been correlated with taste acuity. This study was undertaken to determine if there is a correlation between taste acuity and salivary zinc levels in hemodialysis (HD) patients and if taste acuity and saliva zinc levels were improved following zinc supplementation. Taste was evaluated by Henkin's forced choice, 3 stimulus, drop technique. Saliva samples were centrifuged and supernatant zinc concentration was determined by flameless atomic absorption spectrophotometry. Six HD patients received 100mg of elemental zinc daily; 6 age and sex-matched controls received placebos daily. Supplementation was provided for 6 weeks. Taste and saliva zinc measurement was conducted pre and post-dialysis, before and after the supplementation period. There was a significant increase in saliva zinc levels post-dialysis after zinc supplementation. Pre-dialysis saliva zinc levels and taste thresholds were not altered significantly by treatment. There were no significant correlations between salivary zinc levels and taste thresholds. Three people developed abdominal discomfort during zinc supplementation and were removed from the study. It was concluded that there is not a significant correlation between salivary zinc levels and taste acuity in HD patients. Taste acuity did not improve after zinc supplementation, although post-dialysis saliva zinc levels increased significantly. This data does not support previous research which demonstrated improved taste acuity with zinc supplementation. It is possible that a larger sample size, increased zinc dose and a longer supplementation period would provide more significant results.

PROSTACYCLIN (PGI_2) SUBSTITUTION FOR HEPARIN (H) IN HEMODIALYSIS (HD). Michael C. Smith*, Kowit Danviriyasup*, Allen E. Cato*, James W. Crow*, and Michael J. Dunn, (intr. by J. Wish). Case Western Reserve Univ., Cleveland, OH and Burroughs Wellcome Co., Research Triangle Park, N.C.

Heparin anticoagulation during HD has been associated with significant hemorrhagic complications. A previous study using dogs suggested that PGI_2 was a suitable substitute for H during HD. Therefore we have compared the safety and efficacy of PGI_2 and H anticoagulation in 5 patients undergoing maintenance HD. PGI_2 infusion at 4-12 ng/Kg/min produced no consistent changes in bleeding time, prothrombin time or partial thromboplastin time. During PGI_2 HD, 1 patient showed a progressive inhibition of platelet aggregation and 3 demonstrated a progressive decrease in ADP-stimulated thromboxane B_2 production in vitro. Mean plasma 6-oxo-$PGF_{1\alpha}$ (stable product of PGI_2) levels at 0, 1, 2 and 3.5 hr. of HD and 2 hr. post HD were 60, 990, 1890, 2600 and 170 pg/ml respectively. Plasma concentration of 6-oxo-$PGF_{1\alpha}$ increased as a function of the total dose of PGI_2. When PGI_2 HD was compared to HD with H there were no significant differences in intradialytic changes of serum electrolytes, divalent cations, uric acid, liver function tests, hematocrit, leukocyte count, platelet count, pH, pCO_2 or pO_2. Post HD BUN and Cr decreased 45% and 36% with PGI_2 but only 37% and 29% respectively with H. Transient hypotension occurred in 1 patient during PGI_2 HD and responded promptly to a reduction in the PGI_2 infusion. No other untoward effects of PGI_2 were noted.

These preliminary results indicate that PGI_2 is an effective and safe alternative to H anticoagulation during HD.

DRAINAGE VOLUMES, CLEARANCES, GLUCOSE ABSORPTION AND PROTEIN LOSSES IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS, M. Sorkin, K. Nolph, B. Prowant,* H. Moore,* Department of Medicine, University of Missouri, Columbia, Missouri

Because continuous ambulatory peritoneal dialysis (CAPD) is becoming widespread, it is important to establish norms for drainage volumes (V, ml), clearances (ml/min) of urea (Curea), creatinine (Ccr), and inulin (Cin), and concentrations in drainage of glucose (G, mg/dl) and protein (P, mg/dl). We have monitored these in 908 two-liter exchanges (ex) from 33 adult patients over 3 1/2 years of our CAPD program. Exchanges collected (all in the absence of peritonitis) included those with solutions containing 1.5% or 4.25% glucose and with cycle times of 4 or 8 hours. Most patients used 8 hour cycles overnight. Mean values during training were: (n=number of exchanges)

Type	V	Curea	Ccr	Cin	G	P	n
1.5%-4 hr.	2209	7.5	5.4	2.2	586	90	525
1.5%-8 hr.	2132	3.8	3.1	1.3	363	164	53
4.25%-4 hr.	2819	9.2	7.3	3.1	980	86	152
4.25%-8 hr.	2763	5.1	4.1	1.7	564	121	63

Curea approaches flow rate. Standard errors of all mean clearances reanged only 0.1-0.3. No trends for change from these measurements during training have been identified with time on CAPD even with recurring peritonitis. Two patients with consistently low clearances and P had pervious severe hypertension. G falls more than 50% in all ex types, P increases with time but not with ultrafiltration. Summary: Deviations from these norms may suggest vascular or peritoneal disease and require changes in diet or exs/day. CAPD per se does not cause changes.

LONGITUDINAL HEPATITIS (H) PROFILES IN DIALYSIS PATIENTS (P). AP Swamy, RVM Cestero, J Nusbacher*, Monroe Comm Hosp, Univ of Rochester, & Am Red Cross Blood Services, Rochester, NY.

HB surface antigen (HBsAg), antibody (HbsAb), core antibody (HbcAb), and HA antibody (HAAb) detect prior HA and HB infection. A retrospective and prospective analysis was done of H profiles of 64 DP, aged 15-82 ($\bar{x}$=46±16) with duration of D ranging from 12-132 mos; ($\bar{x}$=45±26 mos; 240 P yrs). Only frozen red cells were transfused. HbsAg and HbsAb were reviewed from start of D. Prospectively, HbsAg, HbsAb, HbcAb, and HAAb were done $\leq$q6wks X 12 mos. Stored specimens from start of each P's D were also tested. Liver function tests (LFT), were done $\leq$6wks during entire D course. On entry all P were HbsAg negative (-), but HbsAb, HbcAb, and HAAb were positive (+) in 15(23%), 15(23%), and 36(56%) P respectively. From start of D HbsAb(+) in titer $\leq$ 8 appeared in 4 P without LFT or HbsAg/HbcAb change. (+) HAAB developed in 2P. LFT were abnormal (abn) sometime during D course in 24/64(38%) P. 1/24 developed HbsAg(+) with clinical findings, and (+) LFT. P subsequently converted to HbsAg(-) with high HbcAb and HbsAb titer. In 6/24 another cause for abn LFT was found. 4/24 had unexplained abn LFT for $\geq$ 1 mos; 13/24 had 1 episode each of abn LFT which lasted $\leq$ 1 mo. 23% of P beginning D have evidence of prior HB infection. (Normal = 12%). HAAb prevalence is similar to normals. The HbsAb titer $\leq$ 8 in 4P without HbsAg/HbcAb or abn LFT may suggest immunologic improvement after adequate D. HB in 1 P was probably transfusion related since donor later showed HbcAb(+) and HbsAb(+). The low incidence (1/64) of definite change in HB markers after starting D suggests that subclinical HB infection in D P is rare when frozen blood is used.

ETHANOL (EtOH) AND DIALYSIS (D) PATIENTS (P). AP Swamy, RVM Cestero, R. Kaser*, VK Jain. Monroe Community Hospital, Univ. of Rochester, Roch, NY

Reports by P of changes in taste and tolerance for EtOH prompted a study of EtOH metabolism in D P. A uniform questionnaire was given to 32 P about subjective changes in tolerance, taste and side-effects such as headache, nausea and fatigue before and after onset of renal failure. Oral EtOH (0.5 Gm/Kg) was given to 5 normal controls (C) and 10 D P (5 pre-D and 5 post-D) after a 4 hr fast. Blood EtOH, Na, K, Cl, HCO_3, and glucose (G) were measured at 0,15,30,60,90, and 120 min. EtOH was analyzed by gas liquid chromatography. Decreased (↓) EtOH tolerance after beginning D was noted by 20/32 (60%) P; 10/32 (30%) noted loss or alteration of taste; 10/32 reported increased (↑) side effects. Table shows EtOH levels in Mg/dl (x±S.D.)

	0	15	30	60	90	120
C	0	15±8	36±6	48±7	36±8	27±12
Pre D	0	16±7	36±15	45±7	36±3	30± 2
Post D	0	13±10	36±17	40±11	34±9	28± 7

In all P&C blood EtOH peaks at 30 min and declines gradually. EtOH concentrations between P&C do not differ at any time. G peaks at 30 min in C (46%↑) and pre-D P; (30%↑); it does not change in post-D P. HCO_3 ↓, reached nadir at 30 min, (10%↓). G and HCO_3 returned close to baseline by end of study period. K ↓ in C and pre D P but ↑ in post DP. P report ↓ tolerance, altered taste, and ↑ side-effects to EtOH. EtOH metabolic clearance in D P is similar to C. K, HCO_3 and G show various changes in P&C. Whether the altered symptoms in P are related to these changes or to other metabolic processes needs further study.

VALUE OF GLYCOSYLATED HEMOGLOBINS (GHb) IN DIABETIC (DM) DIALYSIS (D) PATIENTS (P). AP Swamy, RVM Cestero, GW Roushey*, Monroe Community Hospital, E. Veverbrants, Univ of Rochester, Roch, NY & K. Eshwar, Arnot Ogden Hosp, Elmira, NY

This study was performed to determine the utility of GHb in management of DM D P and to assess the influence of uremia, transfusions (Tf), and dialysate glucose (G) on the level of GHb. A single survey measurement of GHb was done in 48 stable D P (24DM; 24non-DM). GHb was compared in 10/24 DM P using G dialysate and 14/24 using G free. Seven DM P were followed serially for 15 wks with $\geq$ 3X/wk blood G and 1X/wk GHb. For each P 96±41 blood G measurements were done. Each wk's level of GHb was correlated to the mean G level for the same wk and for each of the preceeding 2 wks. Amount of Tf and blood losses during D were recorded. In the survey, mean GHb in non DM D P = 9.4±1.6%; in DM, mean GHb=11.2±3.5% (normal controls =7.1±1%)($p<.05$). With G dialysate, mean GHb levels =10.9±1.7%; with G free mean GHb =11.5±3.8% (p=NS). Mean weekly blood G ranged from 137±50 to 447±196 Mg/dl. GHb ranged from 7.6%-17.3% ($\bar{x}$=11.3±2.5%). No correlation exists between GHb level and mean G concentration for any of the 3 wkly periods. Twenty-two units of blood were transfused (range0-10/P); no major blood losses occurred. GHb concentration decreased substantially after each Tf (? dilution) regardless of blood G level. GHb levels are ↑ in both DM and non DM D P but the levels in the DM are significantly higher than in non DM. ($p<.05$). Dialysate G does not affect GHb levels. Serial blood G and GHb determinations show no significant correlation in DM P probably because of blood losses and/or Tf. GHb is of doubtful value for monitoring G control in DM D P.

● A DOUBLE-BLIND CONTROLLED TRIAL OF ACETATE VERSUS BICARBONATE DIALYSATE IN ESRD. P. R. Uldall, I.Kennedy,* H.Craske,* E.Porrett,* J.Aid,* F.Woods,* and D.Levine.* Toronto Western Hospital, Toronto, Canada.

Bicarbonate dialysate (BD) is now recognised as being superior to acetate dialysate (AD) during hemodialysis (HD) for many patients (pts) with acute renal failure. It is not yet known whether the majority of stable pts with ESRD would benefit from BD in preference to AD for regular HD. We have conducted a double-blind cross-over controlled trial of BD versus AD in 16 stable pts on 3 X weekly HD for ESRD. BD and AD were delivered on alternate days from an Extracorporeal central system. The 2 dialysates were identical in composition apart from the buffer. Half the pts during the 1st 12 weeks received BD while the other half received AD. Then each group changed to the other mode for a further 12 weeks. All pts at each HD completed standard questionnaires to document dialysis-related symptoms (DRS) with specific reference to nausea, vomiting, headache, cramps, weakness, and dizziness for which a numerical score (NS) was awarded. A similar NS was given to post-dialysis symptoms or well-being on a separate questionnaire. All hypotensive episodes requiring IV saline were recorded. Blood gases, blood acetate, and SMA-12 were estimated in the 1st and last week of each 12 week period 1 hr and 3 hrs after the start of one HD. Results show significantly less DRS in both groups of pts when receiving HD with BD compared with HD with AD ($p < 0.05$). Post HD symptoms and well-being were not different in the 2 groups. Blood gases and standard blood chemistries were not different during the 2 modes. We conclude that since BD causes less DRS, it should be used in HD for ESRD if this can be done reliably.

USE OF THE COX PROPORTIONAL HAZARDS MODEL TO STUDY SURVIVAL IN PATIENTS TREATED FOR END-STAGE RENAL DISEASE. William A. Vollmer*, Patricia W. Wahl*, Christopher R. Blagg. Univ. of Wash. Depts. of Biostatistics and Medicine, and the Northwest Kidney Center, Seattle, Washington.

Survival of patients treated by dialysis and/or transplantation is dependent on many factors, consideration of which is important when comparing results between different treatments or between different centers. We have used the Cox proportional hazards model to compare dialysis and transplant survival in a population of 1038 caucasian patients aged 15 and over, while simultaneously adjusting survival for age, year of first treatment, primary cause of renal failure, and number of associated diseases. Survival of patients with renal failure due to diabetic nephropathy and nephrosclerosis was analyzed separately from that of patients with all other causes of renal failure. No significant difference in survival of patients treated by cadaveric transplantation and by dialysis was observed after adjustment for the above factors, although survival of patients with living related donor transplants was significantly better ($p<0.05$). An improvement in survival was noted in patients with renal failure secondary to diabetic nephropathy or nephrosclerosis treated more recently. This, and other examples, will be used to show how the Cox proportional hazards model permits adjustment for differences in patient populations when comparing survival results for dialysis and transplantation. Survival results from patients treated at different centers can also be compared using this model.

● THE EFFECT OF DIALYSATE SODIUM CONCENTRATION (DNa) AND FLUID REMOVAL ON CHANGES IN PLASMA RENIN, ALDOSTERONE AND BODY FLUID COMPARTMENT VOLUMES DURING HEMODIALYSIS. John C. Van Stone, John Bauer, Jane Carey*. Uni. of Mo., Columbia, Mo.

Fluid removal during hemodialysis with increased DNa is associated with less hypotension and fewer symptoms. To investigate the mechanisms involved 5 stable chronic hemodialysis patients received 6 hemodialysis treatments: 2 each with the DNa 6% greater than, DNa equal to and DNa 6% less than their serum sodium. During one treatment with each dialysate 2 Kg of fluid was removed and during the other treatments weight was kept constant. Total body water (TBW), intracellular water (ICW), extracellular water (ECW) and plasma volume (PV) were determined before and after each treatment. The mean percent change in body compartment volumes, plasma renin (PRA) and aldosterone (ALDO) during hemodialysis are listed in the following table.

DNa	PV	ECW	ICW	PRA	ALDO
		No weight loss			
132	-7.3	-0.8	+0.6	+214	-10
140	-1.4	+1.1	-1.6	+ 89	-26
147	+0.8	+8.6	-6.2	+ 24	-45
		2 Kg weight loss			
132	-21.7	-14.6	+1.5	+298	+71
140	-22.4	-13.2	+0.3	+200	0
147	-14.6	-1.8	-3.7	+ 50	-13

These data indicate that when DNa exceeds serum Na, water shifts out of cells and the reverse is true when serum Na exceeds DNa. With fluid removal loss from PV is disporportionately high. Plasma renin increases during dialysis; low DNa and fluid removal accentuate the increase. Plasma aldosterone tends to decrease during dialysis but fluid removal and low DNa inhibit this decrease.

NUTRITIONAL STATUS IN APPARENTLY HEALTHY HEMODIALYSIS (HD) PATIENTS. M. Wolfson and J.D. Kopple. Portland VAMC and Univ. of Ore., Portland, Ore. & VA Wadsworth MC and U.C.L.A., Los Angeles, Calif.

Although several studies suggest that wasting and malnutrition are common in patients (pts) undergoing maintenance HD, these findings are not universally accepted by nephrologists. This may reflect their observations that many HD pts do not seem wasted on superficial inspection and that the former data may have been collected from pts who were indigent, lived alone, or had underlying debilitating illnesses. We, therefore, assessed nutritional status in 13 middle class men undergoing HD at the Portland VAMC. Most appeared to have an excellent clinical response to HD; 4 were home HD pts; and 11 had not been hospitalized for at least one year. Eleven pts owned their own home; all possessed at least one car; mean family income was $20,606; and 12 lived with wives and had at least a high school education. Nutritional status was compared to data from standard tables or values from 60 normal controls. In the HD pts there was decreased triceps and subscapular skinfold thickness, serum transferrin, and C_3 ($p<0.05$ - 0.001 for each comparison). With the exclusion of one obese pt, relative body weight was also reduced ($p<0.001$). Mid-arm circumference, serum IgG, IgA, IgM and C_4 were normal. In 8 of 13 pts serum transferrin and albumin were each more than 2 standard deviations below the mean value for normals. Serum transferrin correlated directly with albumin ($r = 0.69$, $p<0.01$). These data suggest that malnutrition and wasting are not uncommon in HD pts even when they appear to have a successful clinical course.

SLEEP APNEA (SA) DURING HEMODIALYSIS (HD) - A CAUSE FOR HYPOXEMIA AND HYPOTENSION. Melvin Yudis and Robert A. Sirota, Abington Memorial Hosp., Dept. of Med., Abington, Pa.

Recent studies have shown that sleep disordered breathing (SDB) and nocturnal desaturation can occur with both asymptomatic men and postmenopausal women. That such patterns can exist in patients who fall asleep during HD has not been previously explored. We here report a 55 y.o. man with ESRD secondary to diabetic nephropathy who had developed recurrent episodes of SA during HD.

Two of the episodes of SA were associated with hypotension and cardiorespiratory arrest. The latter readily responded to cardiopulmonary resuscitation measures. Later studies during an asymptomatic period revealed moderate hypoxemia.

		pH	pCO_2 A	pCO_2 V	pO_2
	Predialysis (Room Air)	7.36	46		68
2 Liters of O_2	1 Hour	7.31	43		77
	2 Hours	7.34	43	24	113
	3 Hours	7.34	43	26	120

This case may represent a SA syndrome during HD. Such SDB during HD could rapidly worsen the pO_2 creating dangerous hypoxemia. Rapid drops in BP unassociated with volume losses occurred in this patient. Because progesterone has been shown to be a respiratory stimulant, our patient is currently being treated with Medroxyprogesterone acetate 20 mg. t.i.d. plus low flow nasal O_2 during HD.

Further study of SDB occurring during HD is needed to better delineate its importance in contributing to dialysis related hypoxemia and hypotension. Such abnormalities might require treatment with progesterone, O_2, or bicarbonate bath.

ALTERED PERITONEAL CLEARANCE (PC) IN DIABETIC RATS. A.L. Zimmerman*, H.S. Aynedjian*, L.B. Sablay*, L. Walter, N. Bank. Montefiore Hospital & Medical Center, Bronx, New York.

PC in diabetics with ESRD has been reported to be normal or low. To assess early effects of diabetic vasculopathy in the peritoneum, PC of urea (U), inulin (I) and albumin (A) in normal (N), gentamicin nephrotoxic (G) and alloxan diabetic (D) rats were compared. D rats were studied at 2,4 and 6 mos. post-alloxan injection. Two sub-groups of D rats were evident regardless of duration of diabetes: retarded growth with healthy appearance (D_1) and retarded growth or weight loss with muscle wasting and minimal subcutaneous tissue (D_2).

Renal creatinine clearance (Ccr) was calculated pre-dialysis. PD was performed via a Tenckhoff-type catheter with 30 ml warmed commercial dialysate. Exchanges were 15 min with 12 min dwell. Infusions of U and ^{14}C-I were given during dialysis; a bolus of ^{125}I-A was given pre-dialysis. Results (per 100 gm BW; a-$P<0.0005$ to C;b-$P<0.025$ to G;c-$P<0.05$ to G;d-$P<0.0005$ to G;e-$P<0.005$ to G;f-$P<0.0025$ to G;g-$P<0.0025$ to D_2; h-$P<0.025$ to G).

	Ccr ml/min	PC-U	PC-I µl/min	PC-A
C(n=8)	0.435	128	9.9^{b}	0.492^{c}
G(n=6)	0.180^{a}	129	15.0	0.617
D_1(n=5)	0.352^{h}	123^{g}	$10.3^{c,g}$	$0.540^{c,g}$
D_2(n=4)	0.351^{c}	$254^{a,d}$	$28.5^{a,e}$	$1.916^{a,f}$

D_2 rats represent a subpopulation with diabetic vasculopathy involving the peritoneum, as evidenced by increased PC of small, middle and large molecules.

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD) IN CHILDREN. Tariq Zafar* and Donald I. Moel. State Univ. of New York, Downstate Med. Ctr., Dept. of Pediatrics, Brooklyn, New York.

Three children aged 17 months (JQ), 3 yrs (RH), and 6 yrs (KB) were placed on CAPD to define its role in the management of end-stage renal disease in children. They have been followed for 10 wks, 34 wks, and 20 wks and are on an unrestricted diet. The amount of dialysate/exchange was 44ml/kg (JQ), 33ml/kg (RH), and 26ml/kg (KB) determined by the degree of abdominal distension tolerated. The table shows the mean (range) biochemical control achieved:

	J.Q.	R.H.	K.B.
S.Cr(mg%)	2.7(2.1-4.9)	4.1(2.0-5.5)	11.0(5.9-15.0)
BUN (mg%)	36(25-81)	91(40-150)	76(47-100)
S.Ca(mg%)	8.6(7.5-9.6)	9.0(7.4-11.6)	9.7(8.5-10.5)
S.P (mg%)	4.8(2.5-6.4)	7.9(3.1-11.6)	5.7(2.9-7.2)
S.K(mEq/l)	5.3(4.2-6.3)	5.2(3.7-6.8)	4.8(3.0-6.9)
$S.CO_2$(mEq/l)	22(17-32)	25(20-32)	30(24-40)
Hct (%)	28(22-47)	24(17-32)	22(20-25)

where S.Cr is serum creatinine; S.Ca is serum calcium; S.P is serum phosphorus; S.K is serum potassium; $S.CO_2$ is serum bicarbonate; and Hct is hematocrit. The incidence of blood transfusion was 1/10 patient wks (JQ), and 1/6.8 patient wks (RH). Patient KB required no blood. Incidence of peritonitis was 1/10 patient wks (JQ), 1/6.8 patient wks (RH), and 1/20 patient wks (KB). Patient RH developed bilateral inguinal hernias. He also grew 3.5cm and gained 1.3kg since the start of CAPD. The other patients have also grown. The preliminary data shows that CAPD can be used with success in children. Major problems appear to be the low amount of dialysis fluid/exchange, and the high incidence of peritonitis.

PROSTACYCLIN CAN TOTALLY REPLACE HEPARIN DURING HEMODIALYSIS. Randall M. Zusman, Robert H. Rubin,* and Nina Tolkoff-Rubin. Medical Services, Massachusetts General Hospital, Boston, MA.

Prostacyclin (PGI_2) is a potent vasodilator and inhibitor of platelet aggregation. To assess the clinical utility of PGI_2 as an anti-platelet agent in extracorporeal circuits, 10 patients with chronic renal failure (creatinine clearance less than 10 cc/min) underwent hemodialysis (D) (Extracorporeal coil dialyzer with bicarbonate-containing dialysate) with PGI_2 in the total absence of heparin (H). Each patient received an intravenous infusion of PGI_2 at 4 ng/kg/min for 10 minutes prior to D. PGI_2 was infused into the arterial line of the dialyzer at an initial rate of 4 ng/kg/min and was adjusted to maintain blood pressure and minimize side effects. Each patient completed 240 min of D and received a total of 423 ± 96 ng PGI_2/kg (mean ± S.E.M.) (range:55-780). The duration of PGI_2 infusion into the dialyzer was 181± 27 min but varied from 34-240 min. The rate of PGI_2 that maintained a stable blood pressure and prevented platelet aggregation ranged from 0.25 to 4.0 ng/kg/min. During D, the blood urea nitrogen and creatinine fell from 77± 7 to 39± 4, and 13.4 ±1.7 to 7.8 ± 1.1 mg/dl, respectively. The platelet count, prothrombin time, partial thromboplastin time, and activated clotting time were unaffected by PGI_2. There were no differences in the changes in blood urea nitrogen, creatinine, potassium, or calcium during D with PGI_2 compared with control D performed with H. During D with PGI_2 some patients reported headache, flushing, nausea, and abdominal pain but these effects disappeared with a decrease in PGI_2 infusion rate. Clotting within the dialyzer did not occur. We conclude that PGI_2 can totally replace H during D and that PGI_2 might be therapeutically preferable to heparin for hemodialysis of patients who have a contraindication to anticoagulation.

Hypertension

HEMODYNAMIC PROFILES IN 1-YR-OLD DOGS WITH NEONATALLY-INDUCED COARCTATION HYPERTENSION (NICH). S.P. Bagby and G.M. Baur*, VA Med. Ctr. & Univ. Ore. Health Sci. Ctr., Portland, Ore.

In awake dogs with NICH and in littermate controls, we measured hemodynamic indices on normal Na^+(NS) diet, and, after Na^+ depletion (low Na^+ diet + Lasix^R), before and 15 min after converting-enzyme inhibitor (CEI:SQ20881, .5mg/kg bolus in 9 dogs; SQ14225, 300mg/kg load + 5 ug/kg/min in 4 dogs). Results (mean ± SEM) for brachial mean pressure (MAP), cardiac output (CO) by dye dilution, total vascular resistance (TVR), stroke volume (SV), and heart rate (HR) are:

	(n)	MAP mmHg	CO cc/m/kg	TVR units	SV cc/kg	HR beats/m
NS Diet						
NICH	5	138±6	135±10	2724±267	1.48±.10	93±6
Cont	4	112±5	109± 4	2758±497	1.38±.12	81±6
Low Na/Lasix						
Pre-CEI						
NICH	9	128±5	137± 9	2612±135	1.29±.07	106±6
Cont	6	107±6	124± 4	2181± 96	1.34±.08	94±6
Post-CEI						
NICH	8	112±7	174±15	1827±127	1.51±.09	115±6
Cont	5	89±5	155±17	1511±168	1.47±.12	105±5
p(NICH)		<.001	NS(<.10)	<.05	NS	<.05
p(CEI)		<.001	<.005	<.001	NS	<.01

Overall, NICH exhibited increased HR and TVR with a tendency toward increased CO. Whereas ↑CO and normal TVR characterized NICH on NS diet (4/5 dogs), patterns varied on low Na^+/Lasix (4/9 ↑TVR, 3/9 ↑CO, 2/9 ↑both). CEI caused similar hemodynamic responses in NICH and controls. We conclude that 1-yr NICH exhibits hemodynamic heterogeneity and intact cardiac functional reserve under hypotensive stress. The 4-5% volume excess shown previously in NICH is not consistently accompanied by ↑CO.

DISTRIBUTION OF ANGIOTENSIN I (AI) AND II (AII) IN DOG KIDNEY. R.L. Baranowski, C. Westenfelder, E. Stuart* and N.A. Kurtzman, (intr. by Luis Guitierrez). Univ. of Illinois, Chicago, Illinois.

We have previously demonstrated the presence of intrarenal AI and AII in rat kidney. It has been assumed that these measurements reflect renal cortical levels of angiotensin since renin is found only in renal cortical tissue. Recently, however, an enzyme called "tonin" has been described which is capable of generating angiotensins in vitro. The highest concentrations of this enzyme have been reported in the renal papilla and medulla. To explore the possibility that angiotensins may be generated in situ by renal medullary and papillary tissues, angiotensin peptides were extracted from all parts of the dog kidney with 80% ethanol, then concentrated on Dowex 50 X-4 resin and quantified by radioimmunoassay of AI and AII. The following table shows the values from kidneys obtained from 13 normal dogs. Mean values ± SEM are expressed as pg of angiotensin per gram of tissue.

	AI (pg/gm)	AII (pg/gm)	AI/AII
Cortex (n=13)	1,121±333	871±159	1.2
Medulla (n=13)	317±72	409±60	1.3
Papilla (n=10)	312±57	259±81	0.8

These data demonstrate that renal medullary and papillary tissues generate AI and AII. A possible physiologic role for extra-cortical angiotensin biosynthesis may include the regulation of medullary blood flow and the stimulation of prostaglandin secretion. The mechanism whereby extra-cortical tissues produce angiotensins is presently unknown.

URINARY KALLIKREIN(UK)AFTER RENAL TRANSPLANTATION (RT):FINDINGS IN HYPERTENSIVE(HT)VERSUS NORMOTENSIVE(NT)GRAFT RECIPIENTS;LIVING RELATED DONOR(LRD) VERSUS CADAVERIC(CAD)GRAFTS;AND ACUTE REJECTION (AR)VERSUS ACUTE TUBULAR NECROSIS(ATN). A Barg,* F Vincente, W Amend, DT O'Connor. Depts of Med, VA Hosp. & Univ. of Calif.,San Diego and San Francisco, CA.

We studied UK excretion, a putative marker for a renal vasodilator and natriuretic system, in 29 patients after RT and compared the results to those in normal controls (C,n=18) and patients with renal parenchymal disease (RPD,n=14). Patients were subdivided into HT(n=15) vs NT(n=14) recipients after RT; LRD(n=20) vs CAD(n=9) recipients; those developing AR(n=8) vs ATN(n=9). 24-hour urine was collected and UK measured radiochemically in EU/24h. Results expressed as mean ± SEM.

Kallikrein Excretion, EU/24h

HT 5.1 ± 1.7 LRD 13.9 ± 3.6 AR 5.4 ± 1.6
NT 15.4 ± 4.9 CAD 2.7 ± 0.4 ATN 1.2 ± 0.3

RT patients excreted 10.5 ± 2.7 EU/24H vs 18.7 ± 2.3 for C subjects and 1.9 ± 0.5 for RPD patients.

We conclude: 1) RT patients excrete UK even with nephrectomy prior to RT. 2) RT patients excrete less UK than C subjects and more UK than RPD patients. 3) HT patients excrete less UK than NT patients. 4) LRD recipients excrete more UK than CAD recipients. 5) AR patients excrete more UK than ATN patients. 6) Alterations in UK may be involved in the pathogenesis of HT, AR, and ATN after RT.

● ANGIOTENSIN II RECEPTORS IN MESANGIAL CELLS CULTURED FROM RAT RENAL GLOMERULI. L. D. Barnes,* M. N. Guy,* M. D. Lifschitz, and J. I. Kreisberg. Univ. of Tx. Hlth. Sci. Ctr., Depts. of Biochemistry, Medicine and Pathology, San Antonio, Tx.

Angiotensin II (AII) alters glomerular filtration parameters through interaction with specific AII receptors within the renal glomerulus. Previous studies indicate that AII interacts with mesangial cells. ^{3}H-AII is autoradiographically detected over mesangial cells following injection of ^{3}H-AII into rats. Cultured mesangial cells contract when incubated with 1 nM AII. We have investigated the basic binding characteristics of ^{125}I-labeled AII (^{125}I-AII) to mesangial cells cultured from rat renal glomeruli. Mesangial cells were incubated in 100 mM sodium phosphate, pH 7.4, 50 mM NaCl, 1% BSA, and ^{125}I-AII. Bound and free ^{125}I-AII were separated by filtration through glass fiber filters. Non-specific binding was determined by inclusion of 10^{-4} molar excess unlabeled AII. Equilibrium binding of 65 fmole ^{125}I-AII per mg of cell protein was attained in 20 min at 24°C at an initial concentration of 0.7 nM ^{125}I-AII. Addition of excess unlabeled AII caused displacement of 50% of the bound ^{125}I-AII within 5 min. Binding of 0.5 nM ^{125}I-AII to mesangial cells was linear from 10 to 60 µg cell protein. des Asp^1-AII (AIII) at 10^{-4} molar excess completely blocked ^{125}I-AII binding, while epinephrine, insulin, glucagon, ADH and isoproterenol at 10^{-4} molar excess had no effect upon ^{125}I-AII binding. ^{125}I-AII binding is rapid, reversible, specific and occurs at concentrations similar to circulating AII in vivo. These data indicate that the AII binding sites present in cultured mesangial cells represent physiologically important receptors, and support the hypothesis that AII regulates parameters of glomerular filtration by binding to and inducing contraction in mesangial cells within the glomerulus.

● ACUTE AND CHRONIC EFFECTS OF DIURETIC THERAPY ON BODY FLUID COMPOSITION. John H. Bauer and Charles S. Brooks*, Truman VA Hosp. and Dept. of Medicine, University Missouri Medical Center, Columbia, MO.

Although diuretics acutely effect reductions in extracellular fluid (ECF), their chronic effect is controversial. In the current study, determinations of plasma volume (PV) by ^{125}RISA, ECF by $Na_2{}^{35}SO_4$, and total body water (TBW) by ^3H_2O were made in 19 male hypertensive subjects following 3 weeks of placebo, 24 hrs of diuretic Rx, 2 mo of diuretic Rx, and 2 wks following withdrawal of diuretic Rx. Mean results are indicated below:

	placebo	acute-D	chronic-D	withdrawal
PV (L)	3.2	3.1	3.3†	3.5ϕ
ISF[1] (L)	14.5	13.6†	13.1	15.2ϕ
ECF (L)	17.7	16.7††	16.3	18.6ϕ
ECFxNa[2]	2505	2354†	2308	2620ϕ
ICF[3] (L)	31.8	31.1	31.2	30.6
TBW (L)	49.4	47.9ϕ	47.6	49.2††
Wt (kg)	94.7	92.4ϕ	92.7	94.1†

†p<0.025, †† p<0.01, ϕp<0.005 compared to previous period; D=diuretic Rx; [1]ISF=interstitial fluid = ECF-PV; [2]ECFxNa=mEq ECF sodium = ECF (L) x serum Na (mEq); [3]ICF=intracellular fluid = TBW-ECF.

Acute diuretic Rx produced reductions in blood pressure (BP)(from 150/99 to 136/90), ISF, ECF, ECFxNa, TBW and wt. Chronic diuretic Rx maintained reductions in BP (132/87), ISF, ECF, ECFxNa, TBW and wt. PV returned to placebo value. Withdrawal of diuretic Rx produced rebound in BP (to 150/95), TBW and wt, and overshoot in PV, ISF, ECF and ECFxNa. Volume overshoot could not be attributed to persistant activation of the renin-aldosterone system, or increased salt intake. We conclude that chronic antihypertensive effects of diuretic Rx are associated with sustained reductions of salt and water within the ISF.

● ABNORMAL RELATIONSHIP BETWEEN SODIUM (Na) INTAKE AND PLASMA NOREPINEPHRINE (NE) IN SALT-SENSITIVE PATIENTS WITH ESSENTIAL HYPERTENSION (EH). V.M. Campese, M.S. Romoff, D. Levitan, Y. Saglikes,* R.M. Friedler, and S.G. Massry. Div. Neph., Dept. Med., USC Sch. Med., Los Angeles, CA.

The activity of sympathetic nervous system as estimated by plasma NE is suppressed by high Na intake. The worsening of blood pressure by high Na in EH may be due to an abnormal relationship between Na and sympathetic nervous system. Twenty patients with EH and 10 normal subjects (NS) were studied for 3 weeks in a metabolic ward and while receiving either 10, 100 or 250 mEq/day for a week in a randomized sequence. With high Na, mean blood pressure (MBP) did not change in NS and in 8 patients with EH (Na-resistant) but increased by at least 10% (16±2 mmHg) in 12 patients (Na-sensitive). The latter change was not due to greater Na retention since weight gain was not different from NS or Na-resistant EH, nor due to abnormal Na-renin relationship since PRA was reduced in all. There were no significant differences in NE among NS or EH patients while on low Na. High Na reduced NE from 22±3.4 to 12±2.3 ng/dl in NS ($p<0.01$ paired analysis) and from 17±4.5 to 12±2.4 ng/dl in Na-resistant patients ($p<0.05$). In contrast, NE did not fall with high Na in the Na-sensitive patients (20±1.9 vs 22±3.2 ng/dl) despite adequate suppression of PRA. The data demonstrate that: 1) twelve of 20 patients (60%) with essential hypertension are sensitive to high sodium intake and respond by significant elevation in their MBP, 2) this phenomenon is most probably due to abnormality in the relationship between sodium intake and plasma norepinephrine.

● SPECIFIC STIMULATION OF RENIN BY PGI_2 IN ISOLATED RAT GLOMERULI. W. H. Beierwaltes, S. Schryver,* E. Arne,* J. Strand,* and J. C. Romero. Dept. of Physiology, Mayo Clinic, Rochester, MN.

A direct interaction between renin release and renal prostaglandin (PG) synthesis has been demonstrated in an in-vitro preparation of isolated rat glomeruli (ASN 66A, 1979). However, the specific PG mediating renin release remains unknown. This study was designed to determine; a) which PG's are synthesized in isolated glomeruli, and b) which of these PG's specifically elicit renin release. Glomeruli were isolated by a sieving technique and incubated one hour with ^{14}C-arachidonic acid (AA), and the incubation media run on TLC to determine the profile of endogenous PG synthesis. Six % conversion of AA produced 42% PGE, 17% $PGF_{2\alpha}$, 20% PGD_2, 6% thromboxane (Tx) A_2 and 15% PGI_2. To determine which of these PG's may stimulate renin release, glomeruli were suspended in glass chambers and perfused with modified Kreb's Ringers at 0.3 ml/min (pH 7.4). The effluent was collected in 10 min fractions and assayed for renin by radioimmunoassay. The exogenous administration of 2.8×10^{-8}M PGE_2, $PGF_{2\alpha}$, PGD_2, TxA_2 and a stable analogue of PGH_2 did not alter renin release, while 1.6×10^{-4}M AA increased renin from 5.9±1.1 to 12.0± 2.9 ng AI/ml/hr ($p<0.05$). Because of its short half-life, 2.8×10^{-8}M PGI_2 was perfused in Kreb's at pH 9.4 where it remains stable. Basal renin increased to 8.1±1.9 but renin increased in response to PGI_2 (to 14.8±2.6, $p<0.005$). A similar infusion of PGE_2 at pH 9.4 had no effect upon renin. These results suggest that the direct interaction between renin and PG seen within isolated rat glomeruli is due uniquely to the action of PGI_2 and is exclusive of the other glomerular PG's.

INCIDENCE AND SIGNIFICANCE OF HYPOMAGNESEMIA IN TREATED AMBULATORY HYPERTENSIVE PATIENTS. Steven G. Chrysant, Robert Whang, Bonnie L. Dillard*, and Walter J. Smith*, Univ. of Okla. and Vet. Adm. Med. Centr., Okla. City, Okla.

Hypomagnesemia (HM) has been reported in pts with essential hypertension (EH) and with the use of diuretics. Diuretics constitute the core of any antihypertensive regimen. However, the incidence of HM in treated pts with EH and its role in the control of BP are not known. The BP in the sitting (S) and upright position (UP) and a blood sample in the fasting state were taken from 1000 treated pts with EH. The blood was analyzed for Mg^{++}, Ca^{++}, PO_4, Na^+, K^+, BUN, creatinine and uric acid. Based on results, the pts were divided in 4 groups. Group 1 (low Mg^{++}, low K^+) 20 pts or 2%; Group 2 (low Mg^{++}, normal K^+) 25 pts or 2.5%; Group 3 (normal Mg^{++}, low K^+) 150 pts or 15%; Group 4 (normal Mg^{++}, normal K^+) 805 pts or 80%. Group 1 pts had lower Ca^{++} than the other 3 groups ($p<.01$). No significant difference in BP (S+UP), Na^+, PO_4, BUN, creatinine or uric acid were found between the 4 groups of pts. Pts in Groups 1 and 2 required more drugs for the same degree of control of BP than Groups 3 and 4 ($p<.05$). The data indicate: 1) The incidence of HM in treated pts with EH is 4.5% combining Groups 1 and 2. 2) HM may interfere with the hypotensive action of drugs. 3) These observations raise the question as to the future role of supplementary Mg^{++} in the treatment of hypertension of pts prone to HM.

DIETARY CALCIUM (Ca) INTAKE IN NORMAL (NL) AND HYPERTENSIVE (HTN) HUMANS. Clarice Cole,* Cindy Morris,* and David A. McCarron (Intr. by Charles Plamp). Univ. of Oregon Hlth. Sci. Ctr., Div. Nephrol., Portland, Oregon.

Sodium and potassium intake have been widely studied in HTN subjects; however, little is known about dietary Ca, even though Ca is critical to NL cardiovascular function. Recent reports have noted abnormalities of Ca metaboilsm in humans and experimental hypertension. Using a protocol involving weekly questionnaires and 24 hour recalls, we determined daily averages for total Ca, total dairy Ca, % dairy Ca and fluid milk intake in 34 NL and 39 HTN subjects.

HTN's total Ca (693 mg, $p<.06$), dairy Ca (405 mg, $p<.001$) and % dairy Ca (64%, $p<.005$) intakes were significantly less than the NL's (total 887 mg; dairy 659 mg; %, 79%). There was no significant difference in estimated Na+ intake. The total Ca, dairy Ca and % dairy Ca intake of the NL's were similar to estimates from previous surveys of NL populations. With increasing age, NL's total Ca ($r=-.38$, $p<.01$) and milk intake ($r=-.40$, $p<.01$) declined; however, their total dairy Ca intake was unchanged and the % dairy Ca actually increased ($r=.31$, $p<.05$). In contrast, with increasing age the HTN's total Ca and milk intake did not change; however, their % dairy Ca decreased ($r=-.26$, $p<.05$) further.

In summary: 1) HTN's total Ca, dairy Ca and % dairy Ca intake is less than NL subjects; 2) the difference is most pronounced at younger ages; 3) with increasing age, % dairy Ca consumption is significantly less in the HTN. We conclude that these findings may have important pathogenetic and therapeutic implications for HTN subjects.

TWO-PHASE HEMODYNAMIC RESPONSE TO 8-ARGININE-VASOPRESSIN IN HEALTHY MAN. Kilian Glänzer*, Birgit Prüßing*, Rainer Düsing, and Herbert J. Kramer. Med. Univ. Poliklinik Bonn, West Germany

In the present study we infused arginine-vasopressin (AVP) in seven healthy volunteers at doses of 30 and 160 pmoles per min, respectively, resulting in mean plasma AVP concentrations of 41 ± 1.7 and 207 ± 43.7 fmol/ml. During the first 20 min only a small transient and statistically insignificant increase in blood pressure (BP) was observed. Cardiac index (CI) measured by impedance cardiography decreased by 11 and 22%, respectively, mainly due to a decrease in in stroke volume (Δ SV: -3.3%) and heart rate (Δ HR: -9.3%). All hemodynamic parameters returned to preinfusion values within 20 min, although maximal plasma levels were not yet reached. AVP infusion suppressed plasma renin activity from 1.49 ± 0.77 to 0.87 ± 0.43 ng/ml/3h. Pretreatment with indomethacin did not affect magnitude or time course of the early hemodynamic changes (ΔCI: -14%, Δ SV: -13%, ΔBP: +2%) and late BP regulation. In contrast to our previous findings in asympathetic patients (J. Cardiovasc. Pharmacol. 1980) the vasoconstrictor effect of AVP is antagonized in the early phase via the cardiovascular reflex system. Thereafter, other hemodynamic, nervous, or hormonal counterregulations must be postulated. A role of the endogenous prostaglandin system seems unlikely.

DIFFERING EFFECTS OF BETA-BLOCKING THERAPY ON RENAL HEMODYNAMICS. Gerald R. Dreslinski, Franz H. Messerli,* Francis G. Dunn, Daniel H. Suarez, Efrain Reisin, Edward D. Frohlich.* Ochsner Medical Institutions, New Orleans, Louisiana.

Systemic (dye dilution) and renal (I^{131} para-aminohippurate) hemodynamics were studied in 2 groups of patients with mild essential hypertension treated (Rx) with beta-blocking drugs: 11 with acebutolol (AC), and 10 with atenolol (AT) for 4 weeks. Results were:

	AC Control	%Δ(Rx)	AT Control	%Δ(Rx)
MAP(mmHg)	105±7	-5	109±16	-9*
CI(L/min/m^2)	3.49±0.90	-10	3.37±0.46	-21*
TPR(units)	32.0±6.0	2	32.6±5.3	15*
RBF(ml/min/m^2)	641±69	-16*	461±82	8
RVR(units)	16.8±1.8	14	24.9±8.0	-16*
PRA (ng/ml/hr)	0.72±0.27	-54	0.66±0.28	-43
GFR (ml/min)	122±9	-1	107±13	-5

(mean± S.D.); *$p \leq 0.05$;
MAP=mean arterial pressure; CI=cardiac index; TPR=total peripheral resistance; RBF=renal blood flow; RVR=renovascular resistance; PRA=plasma renin activity; GFR=glomerular filtration rate.

Disparate renal hemodynamics occurred independent of systemic changes, while GFR was preserved and PRA reduced by both agents. Differences in cardioselectivity, intrinsic sympathomimetic activity, and/or yet undefined renovascular effects of these agents may explain the dissimilar alterations in MAP, CI, and RBF.

PROSTAGLANDINS PARTICIPATE IN THE REGULATION OF NaCl ABSORPTION IN THE DILUTING SEGMENTS OF THE NEPHRON IN VIVO: EFFECTS OF FUROSEMIDE. Rainer Düsing, Volkmar Nicolas*, Kilian Glänzer*, and Herbert J. Kramer. Med. Univ.-Poliklinik Bonn, West Germany

In the present study, distal delivery (DD) $[(C_{H2O} + C_{Cl})/GFR \times 100]$ and distal fractional chloride absorption (DFA_{Cl}) $[C_{H2O} / (C_{H2O} + C_{Cl})]$ were studied in six healthy volunteers. Studies were performed during intravenous infusion of hypotonic (0.45%) saline (C) and during additional treatment with indomethacin (I), furosemide (F), and furosemide plus indomethacin (F+I). Saline was infused at increasing rates of 0.09, 0.18, and 0.36 ml/min · kg b.wt. each for a 45 minute period. I significantly decreased $U_{PGE_2}V$ from 1.45 ± 0.12 to 0.51 ± 0.09 pmol/min ($p < 0.025$) and $U_{Cl}V$ from 221 ± 29 to 124 ± 19 µEq/min ($p < 0.025$) in the presence of unchanged GFR and DD and a significant increase in DFA_{Cl} from 0.79 ± 0.02 to 0.87 ± 0.01 ($p < 0.002$). F significantly increased $U_{PGE_2}V$ to 2.94 ± 0.34 pmol/min ($p < 0.05$), $U_{Cl}V$ to $2,590 \pm 128$ µEq/min ($p < 0.001$) and decreased DFA_{Cl} to 0.19 ± 0.02 ($p < 0.001$). None of the renal functional changes induced by F was altered during F+I in spite of a marked suppression in $U_{PGE_2}V$. Renal PG participate in the regulation of NaCl absorption in the distal nephron but they do not mediate the tubular effects of furosemide.

VASOPRESSIN DEPENDENT ARTERIAL PRESSURE IN THE RENOPRIVAL RAT. Fernando Elijovich,*Ulana A. Leskiw* and Lawrence R. Krakoff*: (intr. by Ruth G. Abramson). Mount Sinai Hospital, New York, New York.

Participation of endogenous vasopressin (VP) in control of arterial pressure (MAP) and sensitivity to the pressor effect of angiotensin II (A_{II}) were explored in nephrectomized (Nx) and sham-control (C) rats, by means of a VP specific antipressor antagonist, dPMeTyrAVP. Experiments were performed 18 hr after surgery under pentobarbital anesthesia (P) or in the unrestrained-unanesthetized state (U). MAP and dose-response curves to A_{II} were determined before and after dPMeTyrAVP, 50μg/kg iv, (100 times the ID_{50}). Baseline MAP was 133±4 mmHg in P-C and 110±5 in U-C ($p<0.01$). MAP was significantly reduced by dPMeTyrAVP in P-C, 5±2 mmHg, while it did not change in U-C. In Nx rats, MAP was significantly higher in U-Nx, 131±9, than in P-Nx, 89±6. However, MAP reduction by dPMeTyrAVP was 13±2 in P-Nx and 12±2 in U-Nx. Therefore, % reduction in MAP was greater in P-Nx than in U-Nx, ($p<0.01$). Also, MAP reduction by dPMeTyrAVP was greater in both Nx groups than in their respective controls ($p<0.002$). VP antagonism significantly enhanced sensitivity to A_{II} in Nx rats, as assessed by shift to the left in dose-response curves to A_{II}. We conclude that: a) a VP-dependent component of MAP is present in the renoprival state, b) pentobarbital anesthesia does not modify the magnitude of this component in spite of its profound effect on MAP in the renoprival rat, and c) endogenous VP diminishes the pressor action of A_{II}, which is unmasked in the absence of renal renin.

INTRA-RENAL HORMONES AND THE SYNDROME OF HYPORENIN-HYPOALDOSTERONISM (HH). W. Flamenbaum, M. Peck, J.S. Kaufman and R.J. Hamburger. Boston VA Medical Center, Boston, MA.

The syndrome of HH is characterized by hyperkalemic, hyperchloremic metabolic acidosis associated with low levels of plasma renin activity (PRA) and aldosterone (A) secretion. Whether these PRA and A changes are primary or secondary to reduced levels of prostaglandins (PG) and/or kallikrein (KK) is unclear. In the current protocol we examined this by determining the levels of PRA, A, PG-E (by radioimmunoassay) and urinary KK (by an amidase method) in patients with HH as well as in subjects that were either renal function matched (RFM) or PRA matched (PRA-M).

	HH	RFM	PRA-M
n	11	12	12
Cr(mg/dl)	3.6±0.6	3.7±0.4	0.9±0.2
PRA(ngAI·hr·ml)	0.6±0.2	4.2±0.4[a]	0.6±0.1
% inactive renin	81±3	56±2[a]	57±2[a]
Urine A (mg/24hr)	2.2±0.6	20.4±1.1[a]	6.7±0.3[a]
PGE-control	266±84	412±35[a]	449±27[a]
KK-control	0.8±0.4	3.5±0.3[a]	7.5±0.6[a]

(a) different from HH ($P<0.05$)

As compared to the RFM group (without hyperkalemia) all measured parameters were decreased in HH. The decrease in PGE does not appear to be related to altered renal function or low PRA per se. The increased % inactive renin in HH may be related to the low urinary KK. Treatment of HH with fludrocortisone decreased serum potassium concentration and increased KK to 3.9±1.5 mEu/ml, comparable to RFM group but still less than PRA group. These studies appear to exclude a role for KK and do not clearly implicate primary changes in PRA or PG's in the pathogenesis of HH.

EFFECTS OF CAPTOPRIL, DIURETIC, AND THEIR COMBINATION IN LOW-RENIN ESSENTIAL HYPERTENSION. R. K. Ferguson, P. H. Vlasses,* B. N. Swanson,* and J. R. Koplin.* Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Jefferson Medical College, Philadelphia, Pennsylvania.

Six black patients with essential hypertension, 3 males, aged 29 to 59, were selected for study because of low plasma renin activity, mean (±S.D.) PRA, 1.2±0.4 ng/ml/hr, during chronic diuretic treatment. The purpose of the study was to compare the changes in blood pressure (BP), PRA and plasma aldosterone concentration (PAC) before and after chronic treatment with the angiotensin converting enzyme inhibitor, captopril (CAP), and the diuretic, hydrochlorothiazide (HTZ), alone and in combination. Control measurements were made after each patient had been off all medications for at least one week. Mean supine BP was not significantly reduced from control (165/106±7/7 mm Hg) by either HTZ 50 mg/day or CAP 25 mg tid administered alone, but was (146/90±15/7 mm Hg) when they were combined ($P<0.05$); similar treatment differences were noted for standing BP. PRA increased significantly from control (from 1.06±0.6 to 2.12 ng/ml/hr) only on the combination while PAC, body weight and pulse rate did not vary among the treatments. Thus, in these low-renin hypertensive patients, BP could be lowered significantly only by the combination of HTZ with CAP. As the effect of the combination on BP could not be adequately explained via changes in the renin-angiotensin system, additional mechanisms may play an important role in the action of these agents in patients with low PRA.

FUROSEMIDE IS A COMPETITIVE INHIBITOR OF ANGIOTENSIN II. **Arthur E. Freedlender, George J. Trachte,* and Peter D. Candelora,* Univ. of Virginia Med. Sch., Depts. of Urology and Pharmacology, Charlottesville, Virginia.**

Binding of angiotensin II (AII) to a high affinity renal tubule receptor causes cellular sodium extrusion. This action of AII is not mediated by NaKATPase as potassium is also extruded and the response is unaltered in the presence of 7 mM ouabain. To further elucidate the mechanism of this AII stimulated ion transport, ^{22}Na extrusion was measured in isolated rat proximal renal tubules in the presence of furosemide, an inhibitor of NaK cotransport. In the same preparation, the binding of ^{125}I-monoiodo AII was determined. AII mediated ^{22}Na extrusion was reduced to 71±9% and 35±6% of control values in the presence of $10^{-5}M$ and $10^{-3}M$ furosemide respectively. Surprisingly, Scatchard analysis of the binding data revealed an increase in the K_D of the high affinity AII receptor site from 5.9±0.3 nM in control tubules to 4.7±0.2 nM and 2.6±0.4 nM in tubules incubated with 10^{-5} and $10^{-3}M$ furosemide respectively. No differences were observed in the number of high affinity AII receptor binding sites between the furosemide treated and control tubules. Results obtained with angiotensin III, which is equipotent with AII in enhancing renal tubular Na extrusion, were quantitatively similar. The myotropic response to AII was determined by measuring the dose dependent increase in tension generated in rabbit aortic strips. The ED_{50} was increased 10 fold in the presence of 10^{-5} M furosemide. These data suggest that furosemide is a competitive inhibitor of AII and further imply that furosemide induced diuresis may, in part, be mediated by inhibition of the antinatriuretic effect of AII on the proximal renal tubule.

COMMON PATHWAY FOR VASOCONSTRICTOR PROPERTIES OF ANGIOTENSIN (AII), NOREPINEPHRINE (NE) AND VASOPRESSIN (VP). J. Goldberg,* G. Aisenbrey,* M.Levi, T. Berl, and R. Schrier. Dept. Med., Univ. Colo. Hlth. Sci. Ctr., Denver, CO.

AII, NE and VP are known endogenous hormonal vasoconstrictors. In both hypotensive and hypertensive settings, any or all three of these vasoconstrictors may be active, thus identification of a common pathway for their vasoconstrictor properties has important clinical implications. In the present study the in vivo role of transcellular calcium flux in humorally mediated vasoconstriction was examined using two chemically dissimilar inhibitors of cellular calcium uptake, namely nifedipine (Nif, 7.5 µg/kg/min) and verapamil (Ver, 50 µg/kg/min). The pressor effect of AII (0.3 µg/kg/min) was profoundly diminished by both Nif (Control 115 to 155 vs Nif 110 to 120 mmHg, $p<.001$) and Ver (Control 115 to 155 vs Ver 100 to 110 mmHg, $p<.001$). Similarly, the pressor effect of NE was markedly attenuated by both Nif (Control 120 to 150 vs Nif 95 to 110 mmHg, $p<.001$) and Ver (Control 115 to 150 vs Ver 100 to 105 mmHg, $p<.001$). Lastly, the pressor effect of VP was also virtually abolished both by Nif (Control 115 to 160 vs Nif 105 to 110 mmHg, $p<.001$) and Ver (Control 115 to 155 vs Ver 100 to 106 mmHg, $p<.001$). Thus, transcellular calcium flux appears to be a final common pathway for vasoconstriction of AII, NE and VP, a finding with important physiological and pathophysiological implications.

RENOVASCULAR HYPERTENSION: A COMPARISON OF MEDICAL AND SURGICAL THERAPY AFTER THREE YEARS OF FOLLOW-UP. A.P. Harris,* R.P. Russell, P.K. Whelton, P.C. Walsh,* R.I. White,* G.M. Williams,* and W.G. Walker. The Johns Hopkins Hospital, Baltimore, Maryland.

Twenty-five patients (pts) with renovascular hypertension (RVH) have been followed for 36 months (MOS). Eight pts with arteriosclerotic (AS) RVH treated surgically (S) were compared with 8 AS-RVH pts treated medically (M) and 9 pts with fibromuscular dysplasia (FMD) S. All 25 pts had renal vein renin (RVR) ratios ≥ 1.5 and RVR differences ≥ 1 ng/ml/hr. Serum creatinine (CR), diastolic blood pressure (DBP) and the number of pts requiring antihypertensive medication (RX) were determined prior to study (0) and at 12, 24 and 36 MOS.

CR0 and DBP0 were similar in all three groups. FMD pts were all female and younger than AS pts ($p<.01$). DBP12 was significantly ($p<.05$) lower in S-FMD pts than S-AS pts, but DBP24 and DBP36 were similar. RX was required at 36 MOS in 4/9 S-FMD pts as compared to 8/8 S-AS pts ($p<.025$).

When comparing S-AS and M-AS pts there were no differences in DBP or CR at any time during follow-up. Moreover, supplemental RX was required in 7/8 S-AS pts at 12 and 24 MOS and in all 8 S-AS pts at 36 MOS. Thus, in our patients with arteriosclerotic renovascular hypertension medical therapy was as effective as surgical relief of ischemia in preserving renal function and controlling diastolic blood pressure.

DEMONSTRATION OF A PHYSIOLOGICAL ROLE FOR VASOPRESSIN IN THE MAINTENANCE OF NORMAL BLOOD PRESSURE. R.C. Goldszer,* C.A. Andrews,* I. Ichikawa and B.M. Brenner: (intr. by H.G. Rennke). Harvard Medical School, Boston, MA.

We investigated the role of arginine vasopressin (AVP) in the maintenance of mean arterial pressure (AP) in anesthetized Sprague-Dawley rats, utilizing $d(CH_2)_5$ VDAVP, a peptide analogue of AVP synthesized by Dr. M. Manning. An iv bolus of 100 µg of the analogue was effective for at least 3 hours in completely inhibiting the 30-40 mmHg rise in AP which regularly accompanies the infusion of 50 mU of exogenous AVP. This analogue was without effect on urine osmolality either in strong water diuresis or antidiuresis. $d(CH_2)_5$ VDAVP failed to alter AP in 5 water-diuretic rats (from 120±5 mmHg to 119±5); however, this analogue caused an abrupt fall in AP from 112±4 mmHg to 94±4 ($p<.001$) in each of 10 antidiuretic rats. Of note, AP always returned to or toward baseline within 15 min. Pretreatment of antidiuretic rats with saralasin magnified the hypotensive effect of $d(CH_2)_5$ VDAVP (to 70±5 mmHg) and prevented the return to baseline, as did prior bilateral nephrectomy. That prostaglandins (PG) also interact with ADH in the maintenance of AP is indicated by our finding in 6 water-diuretic rats that indomethacin led to a dramatic transient rise in AP (averaging 23 mmHg) in response to doses of exogenous AVP shown to be sub-pressor prior to indomethacin. These studies indicate: 1) that ADH plays an important role in maintenance of AP in the anesthetized, water-deprived rat, and 2) this action of ADH on systemic vascular tone is subject to modification by the renin-angiotensin and prostaglandin systems. Thus, PG not only blunts the antidiuretic effect of ADH, but the pressor response to ADH as well.

PLASMA ALDOSTERONE (PA) LEVELS IN CHRONIC RENAL DISEASE (CRD). Ronald J. Hené,* Evert J. Dorhout Mees,* Hendrik A. Koomans* and Peter Boer* (intr. by Herbert G. Langford). Dept. of Nephrology, University Hospital, Utrecht, The Netherlands.

It has been reported that the increasing fractional excretion of K, necessary to maintain K homeostasis with progression of renal insufficiency, is performed without increase of aldosterone secretion. Recently, (T. Berl et al., Kidney Int. 14:228, 1978) elevated plasma aldosteron (PA) levels were found when creatinine clearance (C_{Cr}) is less than 15 ml/min. Comparison of PA levels can, however, only be done by taking into account the most important determinant: plasma renin activity (PRA). We therefore selected 21 CRD patients with PRA levels within the same normal range, divided into 3 groups according to the degree of renal failure. The results were:

	No.	C_{Cr} ml/min	sK	log PRA	log PA	PA/PRA
Normals	22	78-160	4.4	2.67	2.67	0.93
CRD I	6	21- 70	4.3	2.68	2.92	1.92
CRD II	7	11- 21	4.4	2.49	2.94	3.16
CRD III	8	3- 10	4.4	2.62	3.45	7.20

The differences from normal controls as well as between the groups were significant for PA/PRA ratio as well as for log PA (except between I and II).

It is concluded that at comparable sK and PRA levels, PA becomes elevated when C_{Cr} falls below 50% of normal, which is comparable to results of K loading in normal subjects.

RENAL VASCULAR RESISTANCE (RVR) IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR). C.H. Hsu and J.M. Slavicek*. Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

Cardiac output (CO, ml/min/100 Gm), renal blood flow (RBF, ml/min/100 Gm), mean arterial pressure (MAP, mm Hg), total renal vascular resistance (RVR, mm Hg/ml/min/100 Gm) and mean afferent arteriolar diameter (MAAD, μm) were measured by microsphere method in 8 and 12 wk old SHR and Wistar Kyoto rats (WKY). At least 150 afferent arterioles were identified and the size of microspheres trapped within the arterioles were measured. GFR was measured by inulin clearance (ml/min/100 Gm). The results were:

	Wt	CO	RBF	MAP	RVR	MAAD	Cin
8 wk WKY	161	54.3	5.43	107	20.2	17.3	1.07
(N=4)	±1.9	±4.5	±0.56	±1.0	±1.8	±0.34	+0.08
8 wk SHR	169	33.9	3.06	141	47.5	16.3	1.12
(N=5)	±5.4	±4.5	±0.24	±3.9	±4.0	±0.23	±0.09
p value	NS	=0.06	<.01	<.01	<.01	<.05	NS
12 wk WKY	245	39.7	5.05	119	24.4	19.3	0.83
(N=5)	±8.7	±4.9	±0.52	±4.0	±2.1	±0.12	±0.06
12 wk SHR	248	27.2	2.86	159	56.3	17.4	0.79
(N=5)	±6.9	±2.0	±0.14	±5.5	±4.0	±0.48	±0.10
p value	NS	<.05	<.005	<.001	<.001	<.01	NS

The results demonstrated that MAAD was significantly smaller in SHR compared to controls. RVR of both groups of SHR were 57% higher than those of controls. Since vessel resistance is related to the fourth power of the radius, the decrease in MAAD of SHR contributed 21% (8 wk) and 34% (12 wk) of the increase in total RVR. The remaining increase of RVR presumably occurs in other segmental arteries of the renal vasculature.

THE EFFECT OF ANGIOTENSIN I BLOCKADE ON BLOOD PRESSURE, UTERINE PGE SYNTHESIS, AND FETAL SURVIVAL IN PREGNANT RABBITS. W. Jahnke, E.K. Weir, and T.F. Ferris. Minneapolis, Minnesota.

Captopril, 5 mg/kg, administered intravenously to pregnant rabbits caused a significant reduction in mean arterial blood pressure (MAP) from 102 ± 2.5 to 85 ± 3.6 ($p<.01$) in contrast to non-pregnant rabbits where no change in MAP occurred. In pregnant animals there was no change in cardiac output, uterine blood flow, or renal blood flow following Captopril. Uterine vein plasma renin activity (PRA) was significantly higher than peripheral vein PRA both in the control and experimental period indicating net renin secretion from the uterus and following Captopril PRA increased from 11 ± 3 to 90 ± 19 ng/ml/hr in the uterine vein and from 6 ± 1.6 to 62 ± 15 ng/ml/hr in peripheral vein. A significant reduction in uterine vein PGE concentration occurred during Captopril from 102 ± 17 to 29 ± 9 ng/ml ($p<.01$).

To determine the possible effect of the decrease in uterine PGE synthesis on fetal survival, 21 pregnant rabbits were given Captopril orally, 2.5 or 5 mg/kg/day, from the 15th day of gestation and compared to 12 untreated pregnant rabbits. Eighty-one of 82 fetuses (99%) of the untreated does survived to term, whereas only 24 of the 169 fetuses (14%) of Captopril treated does survived to term.

These studies demonstrate that in the rabbit: 1) the uteroplacental circulation contributes renin to the circulation during pregnancy, 2) in response to Captopril both uterine and renal renin secretion increases, 3) uterine PGE secretion decreases with angiotensin I blockade, 4) Captopril significantly decreases fetal survival. The dependence of uterine PGE synthesis on AII generation suggests possible adverse effects of Captopril during pregnancy.

RENAL FUNCTION AND PATTERNS OF CATECHOLAMINE EXCRETION. Harold D. Itskovitz and Nina Gilberg.* Medical College of Wisconsin, Dept. of Medicine, Milwaukee, Wisconsin

24 hour urinary catecholamine measurements were obtained in 7 normal individuals, 4 patients with pheochromocytoma, and 23 patients with essential hypertension or renal disease. Dopamine was the predominant urinary catecholamine in all patients except those with pheochromocytomas. With increasing degrees of renal insufficiency all catecholamines diminished in the urine, however dopamine excretion decreased to the greatest extent. In patients with good renal function, epinephrine was excreted primarily in its free form whereas norepinephrine and dopamine were excreted primarily as conjugates. With increasing degrees of renal insufficiency an increasingly higher percentage of each catecholamine was excreted as conjugate. Among patients with severe renal insufficiency (serum creatinine ≥6.0 mg/dl) free catecholamines disappeared almost entirely from the urine.

Present data are consistent with a renal origin for the major proportion of urinary dopamine whereas urinary epinephrine and norepinephrine appear to originate primarily from extrarenal sources. When the urinary excretion of epinephrine and/or norepinephrine surpasses dopamine a pheochromocytoma should be suspected. Since the urinary excretion of free catecholamines is diminished markedly in the presence of renal failure measurements of total catecholamines appear preferable in this group to rule out the presence of a pheochromocytoma.

SALT SENSITIVITY OF BLOOD PRESSURE IN CHRONIC RENAL FAILURE (CRF): EVIDENCE FOR RENAL CONTROL OF BODY FLUID DISTRIBUTION IN MAN. Hendrik A. Koomans,* Jan C. Roos,* Peter Boer,* and Evert J. Dorhout Mees* (intr. by Herbert G. Langford). Dept. of Nephrology, University Hospital, Utrecht, The Netherlands.

Blood pressure (BP), extracellular volume (ECV, ^{82}Br space), plasma (PV) and blood volume (BV) and plasma renin activity (PRA) were studied in 23 patients with different degrees of CRF after equilibration on two levels of salt intake. The increase in BP, related to sodium excretion ("salt sensitivity index") was exponentially related to creatinine clearance ($r=-0.89$, $p<0.0001$). On a high salt intake PRA decreased and BV and ECV increased, but the product log PRAxECV (or BV) decreased ($p<0.001$). When divided according to creatinine clearance (gr. I >32 ml.min^{-1}, gr. II <22 ml.min^{-1}), the latter group showed significantly more rise of BP ($p<0.005$) as well as a larger increament of PV and BV ($p<0.05$) for any increase of ECV. The increase of ECV, however, was similar in both groups. Thus, after salt loading PV/IF (interstitial fluid volume) ratio increased in group II and decreased in group I.

It is concluded that salt sensitivity of BP increases with dropping kidney function, and this increase is accompanied by a tendency for a fluid shift from extra- to intravascular compartment. This may point to a decreased tissue compliance in these patients. Moreover the divergence of BP and volume x PRA products after salt loading strongly limits the value of the latter products as BP determinants.

EFFECT OF POTASSIUM DEPLETION (KD) ON THE PLASMA RENIN ACTIVITY (PRA) RESPONSES TO NaCl AND TO ALBUMIN INFUSION. T.A. Kotchen, J.E. Anderson,* J.H. Galla, and R.G. Luke, University of Kentucky College of Medicine, Lexington, Kentucky.

We have demonstrated that inhibition of renin release by NaCl is related to increased Cl^- transport in the thick ascending limb of the loop of Henle (TALH). To evaluate the mechanism of renin stimulation by KD, the effect of KD on renin suppression by acute and chronic NaCl loading and by volume expansion with albumin were studied in the rat. KD was produced by dietary K^+ restriction for 10 days; compared to controls (CON), serum and muscle K^+ were decreased ($p<0.01$). In unanesthetized animals, on a normal NaCl intake, PRA was increased ($p<0.01$) in KD (9.4 ng/ml/hr $\pm$ 0.6 SE) compared to CON (5.0 $\pm$ 0.5). Inactin anesthetized animals were infused with 0.15 M NaCl (5% body wt/60 min), and PRA was suppressed ($p<0.01$) in CON (9.5 $\pm$ 1.6 $\rightarrow$ 4.6 $\pm$ 1.2) but not KD (11.8 $\pm$ 2.8 $\rightarrow$ 12.3 $\pm$ 3.3) rats (n=6/group). Both before and after infusion of NaCl, arterial pressure, inulin clearance, and plasma volume (RISA) in CON and KD did not differ. KD also prevented suppression of PRA and renal renin content by chronic dietary NaCl loading. PRA responses to infusion of albumin (1.0 ml/100 gm body wt/60 min) were also compared in CON and KD rats on low NaCl diets. Pre-infusion PRA was higher ($p<0.01$) in KD (50.3 $\pm$ 7.3) than CON (26.9 $\pm$ 3.2). Volume expansion in the 2 groups was similar and PRA decreased ($p<0.01$) in both groups; after albumin, PRA in KD (14.2 $\pm$ 2.6) and CON (9.5 $\pm$ 1.8) did not differ. Thus, KD prevented suppression of PRA by NaCl but not by volume expansion with albumin. KD may stimulate renin by inhibiting Cl^- transport in the TALH.

LEUKOPENIA ON ORAL CAPTOPRIL THERAPY. Maximo LaMarche, Luis Garcia, Sherrolyn Weed, Prem Kumar, James Pearson, Stephen Leech, Francisco Gonzalez. LSU Medical Center, New Orleans, Louisiana.

Former evidence that captopril (CAPT), a new potent antihypertensive agent causes leukopenia, is inconclusive. The object of this study was to investigate whether CAPT could cause leukopenia in uncomplicated hypertensives. Twelve hypertensive patients (7 females, 5 males) were treated with CAPT alone in dosages ranging from 150 mg. to 450 mg. per day for a period of 14 months. Serial white cell counts (WBC) were done at monthly intervals. Severe leukopenia was defined as total WBC of<3000/cu mm. and moderate leukopenia as 3000 - 5000/cu mm. None of the males developed leukopenia, whereas 5 of 7 females (71.4%) did develop leukopenia of varying degrees. Leukopenia was severe in 2 cases necessitating withdrawal of drug. The changes in 2 cases with severe leukopenia (I) and 3 cases with mild to moderate leukopenia (II) are shown below. Values represent WBC/cu mm. $\pm$ S.D.

	I Severe	II Moderate
Before	5.99 $\pm$1.36	5.99 $\pm$1.36
During	3.88 $\pm$0.72*	4.82 $\pm$1.34*
Peak Fall	2.10 $\pm$0.71*	3.57 $\pm$0.50*
Recovery	3.53 $\pm$0.22	4.03 $\pm$0.55

*Statistically significant p 0.02

We conclude: a) that significant leukopenia occurs after CAPT therapy. b) the leukopenia is reversible. c) the depression of WBC is not dose dependant. d) leukopenia occurs primarily in females. Further studies are in progress to elucidate the mechanism of the leukopenia.

BLOOD PRESSURE RESPONSES TO PHARMACOLOGICAL MANIPULATIONS OF THE KALLIKREIN-KININ SYSTEM (KKS) IN RENAL HYPERTENSIVE RATS: DEPENDENCE ON PRESENCE OF AN INTACT KIDNEY. T. Kushiro,* T.C. Lee, J.P. Girolami,* M. Karam,* N. Yanagawa,* and M.H. Maxwell. Hypertension Service, Cedars-Sinai Med. Ctr., Los Angeles, California.

The functional status of the KKS was assessed in conscious, Na-depleted rats with benign two-kidney, one-clip (2K-1C) as well as two-kidney, two-clip (2K-2C) Goldblatt hypertension to determine whether the presence of an intact kidney may be responsible for the apparent increase in KKS activity previously seen in 2K-1C rats (Lee et al., Clin. Sci. 57: 255s, 1979). The results showed that whereas shamnephrectomy in 2K-1C rats failed to preclude an augmented vasodepressor response (-11.4$\pm$1.2 mm Hg) to kininase II inhibition produced by Captopril (250 ug, iv) during saralasin-induced angiotensin II blockade (10 ug/min, iv) or an augmented vasopressor response (+18.3$\pm$2.4) to kallikrein inhibition by aprotinin (500 KIU/min, iv), contralateral nephrectomy performed under ether anesthesia 90' before completely abolished the augmented responses to both (-1.4$\pm$0.2 and +3.0$\pm$1.2, resp.). Conversely, whereas kininase II inhibition had no effect (-0.4 $\pm$4.4) in 2K-2C rats, it elicited an augmented response (-12.2$\pm$1.9) in the same animals at 18-24 hours after declipping of one renal artery, suggesting that restoration of KKS function may have, in part, been responsible for the significant decline in resting MAP after declipping (from 132.9 $\pm$6.4 to 113.0$\pm$10.9, $p< 0.05$). Accordingly, our results strongly suggest that activation of the renal KKS may constitute an important component of the well-known antihypertensive function of an intact kidney.

HYPERPARATHYROIDISM IS ASSOCIATED WITH HYPERTENSION, AND MAY BE CAUSAL AND IS NOT DUE TO RENAL DAMAGE. H.G. Langford, J.C. Nainby-Luxmoore*, N.C. Nelson*, R.L. Watson*, and T. Barnes*. Univ. of Mississippi Med. Ctr., Dept. of Medicine, Jackson, Mississippi.

The claimed frequency of hypertension in hyperparathyroidism (HPT) ranges from 10% to 70% in various papers. To determine if there is a real relation between HPT and high blood pressure (HBP), a case-comparison study was done of all cases of HPT treated surgically at the Univ. of Miss. Hospital, 1964-1978. 124 cases were identified. Control cases were matched by age-race-sex, days in hospital, and comparable severity of operation. BP on admission of cases was 143 $\pm$ 26.8/89 $\pm$ 13.6 and controls 130.6 $\pm$ 19.8/81.1 $\pm$ 10.8 mmHg, $p<$ 0.001 for diastolic and systolic. "Actual" hypertensives (diastolic $\geq$ 90 mmHg and/or antihypertensive therapy) were cases 90/124 (73%); control 53/124 (43%), $p<0.001$.

Creatinine (Cr) was 1.3 $\pm$ 1.06 in cases; 1.1 $\pm$ 0.53 in controls. When all Cr over 2 were omitted the values were 1.04 $\pm$ 0.35 and 1.03 $\pm$ 0.30. BP of these cases 142.8 $\pm$ 26.9/89 $\pm$ 13.7, n=113, and of controls 130.7 $\pm$ 19.8/81.2 $\pm$ 10.8, n=122, $p<0.001$. BP of all cases postoperatively 125 $\pm$ 16.8/79 $\pm$ 14.3, of controls 126 $\pm$ 16.3/79 $\pm$ 9.3, N.S. BP fall of cases was 17.4 $\pm$ 23.2/9.8 $\pm$ 14.3, $p<0.01$ compared to preoperative. Mean weight of controls was 164 lb. of cases 153.9 lb.

This study suggests that BP in patients with HPT is higher than that found in the general population, that the difference is not due to renal damage as measured by Cr, and that the hypertension may be potentially curable by removal of the parathyroid adenoma.

URINARY KALLIKREIN IS DECREASED BY ANGIOTENSIN I INFUSION INTO THE AUTOPERFUSED RAT KIDNEY IN VIVO. W. LAWTON, J. Shellhase,* J. Voight,* and A. Fitz. V.A. and University Hospitals, Iowa City, Iowa.

Kallikrein (KAL)-Kinin and renin-angiotensin may counter-balance. Angiotensin I (AI) inhibits KAL-esterase in vitro. AI, KAL, UNa+ and UK+ were studied in vivo in the rat. An extracorporeal circuit from the (L) carotid autoperfused an isolated aortic segment supplying the (L) kidney. The (R) kidney was perfused normally. We measured: Mean arterial pressure (MAP; mmHg), Renal Blood Flood, (L), with a flow probe (RBF; ml/min), Inulin clearance (Cin; μl/min/kgx10^3); UKAL (radioimmunoassay; ng/min) and Fractional Excretion of Na+ and K+ (CNa+ or K+/Cin; %): A subpressor dose of AI (50 pg/min) was infused into the (L) kidney. Controls received albumin (BSA).

($\bar{x}$)		Control Rats (n=8)			AI Infused Rats (n=8)		
Period (30 min)		1	2	3	1	2	3
Infusion		BSA	BSA	BSA	BSA	AI	BSA
MAP		121	119	110	123	117	108
RBF		6.9	6.8	6.3	7.6	7.9	7.8
Cin	R	5.6	4.8	4.6	4.3	4.5	3.7
	L	4.4	3.8	3.6	5.0	3.6	3.4
CNa+/Cin	R	.023	.035	.032	.045	.051	.067
	L	.012	.011	.013	.027	.050	.036
CK+/Cin	R	1.5	2.9	3.0	2.8	3.0	4.2
	L	1.6	2.0	2.3	2.0	3.5	3.8
UKAL	R	41	37	37	30	39	32
	L	28	35	36	39	30	29

AI infusion into the (L) kidney in situ is associated with a decrease in UKAL ($p<.05$). This is not related to changes in RBF, surgical preparation or CNa+/Cin. UKAL may be directly related to Cin and inversely related to CK+/Cin. UKAL may be regulated by AI and glomerular filtration rate.

PROSTAGLANDIN E INCREASES RENAL BLOOD FLOW IN THE RAT. Meyer D. Lifschitz, Retta Parma,* Marsha Patton,* Richard W. Osgood,* and H. John Reineck. Dept. of Med., Univ. of Tx. Hlth. Sci. Ctr. and V. A. Hosp., San Antonio, Tx.

Previous studies of the effect of prostaglandin (PG) E on the rat kidney have observed an increase in renal vascular resistance and decrease in renal blood flow. In contrast, studies in the dog and rabbit have regularly yielded increases in renal blood flow. These studies in the rat were performed in isolated perfused kidneys or with intra aortic administration of the PG. Because of the possibility that these results were not solely a reflection of the direct effect of PGE on the rat kidney we devised a technique to administer PGE directly into the left renal artery of the anesthetized rat with no change in glomerular filtration or urine flow rate. A 32 gauge hook needle was inserted directly into this renal artery and renal blood flow was measured directly with an electromagnetic flow probe. PGE_1 and E_2 given at rates from 0.1 - 1.0 μg/Kg/min led to dose related decreases in renal vascular resistance and increases in renal blood flow. Results with both PGE_1 and E_2 were similar. In ten rats given an average dose of PGE of 0.15 μg/Kg/min renal vascular resistance fell 19% from 22.3 to 18.1 ($p<0.001$) and renal blood flow increased from 5.8 to 7.0 ml/min ($p<0.001$). There was no significant change in blood pressure (125 vs. 122 mmHg). These results demonstrate that PGE given directly into the renal artery consistently decreases renal vascular resistance and increases renal blood flow. Thus, the direct effect of PGE on renal hemodynamics in the rat is directionally similar to that found previously in the rabbit and dog suggesting a qualitatively similar receptor-effector mechanism for PGE in all three species.

SEQUENTIAL CHANGES IN THE ACTIVITY OF THE KALLIKREIN-KININ SYSTEM (KKS) IN CONSCIOUS RATS WITH SEVERE CONSTRICTION OF ONE RENAL ARTERY. T.C. Lee, T. Kushiro,* J.P. Girolami,* N. Yanagawa,* and M.H. Maxwell. Hypertension Service, Cedars-Sinai Medical Center, Los Angeles, California.

Studies were undertaken to investigate the possibility that the activity of the KKS may vary as a function of time after unilateral renal artery constriction (RAC). The vasodepressor effect of kininase II inhibition produced by Captopril (250 ug, iv) during saralasin-induced angiotensin II blockade (10 ug/min, iv) as well as the vasopressor effect of kallikrein inhibition by aprotinin (500 KIU/min, iv) were used to assess the functional status of the KKS in four groups (n=5-8) of conscious, Na-depleted rats subjected to either sham-operation or various periods of unilateral RAC with a 0.20 mm i.d. clip. The data (mm Hg; mean $\pm$ S.E.; *$p<0.05$ vs. Sham) are as follows:

Groups	MAP	Captopril	Aprotinin
Sham	95.3+2.3	-1.5+0.6	+9.4+2.5
RAC - 2 wks	114.9+2.7*	-9.0+2.1*	+18.3+2.4*
RAC - 3 wks	158.5+7.1*	-5.3+2.2	+14.0+7.4
RAC - 4 wks	162.1+4.6*	-3.8+0.8	+1.7+1.4

The results show that initial enhancement of the responses to Captopril and aprotinin were followed by progressive and simultaneous declines in both responses as hypertension progressed. Since these augmented responses are abolished by contralateral nephrectomy, these results suggest that the renal KKS may be impaired by the duration and/or severity of hypertension, and the resultant impairment may in turn exacerbate or contribute to the maintenance of hypertension.

MECHANISM OF HYPERRENINEMIA IN THE POTASSIUM DEPLETED (KD) ISOLATED PERFUSED KIDNEY (IPK). S.L. Linas, P. Arnold*, D. Dickmann*. U. Colo. Health Sciences Center, Denver, Colorado.

Dietary KD results in an increase in plasma renin activity (PRA). The mechanism of this effect is not known. In the present study, kidneys from normal rats or from rats made KD by diet were perfused at constant pressure (120 mm Hg) with a Krebs-Ringer-bicarbonate medium containing albumin. KD led to an increase in PRA (3.5 vs 1.1 ng AI/ml/hr, $p<.01$) which was associated with a decrease in macula densa (MD) fluid delivery as estimated by urine flow (70 vs 166 μl/min/gm, $p<.005$) and an increase in renal vascular resistance (RVR) as perfusion flow rate (PFR) was decreased from 34 to 24 ml/min/gm, $p<.005$. The increase in PRA was independent of the MD since PRA could not be suppressed when MD delivery was increased by perfusing KD kidneys with hypooncotic albumin. Moreover when kidneys were made nonfiltering by perfusing with hyperoncotic albumin, PRA remained increased in KD kidneys (8.1 vs 3.5 ng AI/ml/hr, $p<.01$) despite the absence of MD delivery. Since the increase in PRA in both filtering and nonfiltering KD kidneys was associated with an increase in RVR, nonfiltering kidneys were perfused with the vasodilator papaverine. Despite lower tissue K levels in KD kidneys (287 vs 335 μEq/gm, $p<.001$), both RVR and PRA were normalized in KD kidneys perfused with papaverine. In conclusion, PRA is increased in the KD IPK. This increase occurs independently of both the MD and of tissue K levels and is mediated by the renal vascular receptor.

INHIBITION OF RENIN RELEASE (κR) FROM PERFUSED RAT KIDNEY BY VERATRINE (V), MONENSIN (M) AND OUABAIN (O). Alexander G. Logan, and Alice Chatzilias.* Univ. of Toronto, Dept. of Medicine, Toronto, ON.

To determine the importance of transmembrane Na^+ gradient on RR, the effect of three agents which facilitate Na^+ entry into cells was assessed in the absence and presence of manganese (Mn^{2+}) in the perfusate. Mn^{2+} blocks slow inward Ca^{2+} current.

In the isolated perfused rat kidney, V alone caused mild vasoconstriction and raised basal renin concentration. Although isoproterenol (I) stimulated RR in the presence of V with (2.15 ± 0.45) and without (1.47 ± 0.18) Mn^{2+}, compared with I alone (9.15 + 1.69 and 6.74 + 1.56 with and without Mn^{2+} respectively), the mean level was significantly reduced ($p < 0.001$). Mn^{2+} abolished V induced renal vasoconstriction. While M alone had no effect on basal smooth muscle tone or renin level, it significantly attenuated the rise in renin level induced by I with (3.21 ± 0.29) and without (2.48 ± 0.15) Mn^{2+} in the perfusate ($p < 0.01$). O, in the absence of Mn^{2+} (3.23 + 0.21) but not in its presence (5.73 ± 0.99), significantly reduced the rise in renin level evoked by I ($p < 0.01$). O did not induce any significant change in vascular tone.

These results suggest that the action of I on RR appear to be mediated through changes in transmembrane Na^+ gradient since V, M and O attenuated the rise in renin level evoked by I presumably by reducing this gradient. While the inhibitory effect of O depended on extracellular Ca^{2+}, the effect of V and M on RR occurred independent of net Ca^{2+} influx.

THE ROLE OF THE RENIN SYSTEM IN "EXAGGERATED NATRIURESIS". Friedrich C. Luft, Clarence E. Grim, Naomi S. Fineberg*, and Myron H. Weinberger. Indiana University School of Medicine, Indpls., IN.

To examine the role of the renin system in natriuretic responses following saline infusion in hypertensive man, we gave 2L NS over 4hr to 5 patients with 2 kidney renovascular hypertension (RVH) and 7 patients with aldosteronism (ALDO) before (pre) and after (post) operative repair. Plasma renin activity (PRA) and plasma aldosterone (PA) were measured after 2hr upright posture before saline and supine after saline. Creatinine clearance (C_{Cr}) and the fractional excretion of sodium (FE_{Na}) were determined for the 4hr period during saline infusion. Representative data (mean ± SE) are below:

	RVH		ALDO	
	Pre	Post	Pre	Post
Mean BP (mm Hg)	125± 8	109± 5	132± 7	100± 5
Upright PRA (ng AI/ml/3hr)	16± 5	5± 4*	0.7±.2	6± 2*
FE_{Na} (%)	1.6±.5	2.7±.9*	4.6±.7	1.9±.1*

*($p < 0.05$)

In pre RVH upright PRA and PA were correlated inversely with FE_{Na} ($r=-0.9$; $r=-0.8$). Mean BP was not correlated with FE_{Na} in either pre RVH or ALDO. C_{Cr} was not changed in post RVH or ALDO.

Postoperatively: (1) in RVH FE_{Na} increases as PRA decreases despite a reduction in mean BP; (2) in ALDO FE_{Na} decreases as BP decreases and PRA increases. These results suggest that in hypertensive man natriuretic responses to saline infusion are inversely proportional to the level of renin activity and may be mediated by the circulating level of angiotensin II.

PGH_2 ANALOGUE-INDUCED ALTERATIONS IN RENAL HEMODYNAMICS AND SODIUM HANDLING IN THE ISOLATED PERFUSED RAT KIDNEY. Rodger Loutzenhiser*, Murray Epstein and Charles Horton* Nephrology Section, VA Med. Ctr. & Depts. Med. & Pharmacol., Univ. of Miami School of Medicine, Miami, FL.

The stable endoperoxide analogue U-44069 has been demonstrated to be a potent vasoconstrictor in isolated arterial smooth muscle as well as in vivo preparations. We have assessed, therefore, the direct actions of U-44069 upon renal function and renal hemodynamics utilizing the isolated cell-free perfused rat kidney. Media was perfused at a constant pressure of 100 mmHg, perfusate flow being set by the renal vasculature. The PGH_2 analogue produced a dose-dependent (10^{-8}M to 10^{-6}M) decrease in ^{14}C-inulin clearance (C_{In}). Renal perfusate flow (RPF) was reduced only at the highest doses of U-44069. A single bolus administration of 10^{-6}M U-44069 resulted in a prompt sustained reduction in C_{In} from 0.76±0.05 to 0.39± 0.1 ml/min/g (↓48%) and decreased RPF from 39±2 to 34±3 ml/min/g (↓13%). The administration of 10^{-9}M U-44069 increased fractional sodium excretion (FE_{Na}) and distal delivery of filtrate (V/C_{In}) without altering either C_{In} or RPF. The "calcium antagonist", D-600 (10^{-5}M) reversed the U-44069-induced decrease in RPF and C_{In} but did not attenuate the effects of the PGH_2 analogue upon sodium handling. It is concluded that U-44069 produced dose specific effects on the isolated rat kidney. Low doses (10^{-9}M) are natriuretic, possibly due to a direct action upon proximal sodium reabsorption. Higher doses decrease C_{In} and RPF. Reversal of the renal hemodynamic response by D-600 suggests that calcium influx mediates the vascular response.

THE ACUTE CHLORIDE DEPLETION MACULA DENSA STIMULUS (Cl-S) TO RENIN RELEASE (RR) IS BLOCKED BY POTASSIUM DEPLETION (KD). Lyerly, Richard J.*, Luke Robert G., Galla John H., Anderson J.* Kotchen Ted A. Nephrology Res. & Trg. Ctr., Birmingham, Al.

Acute Cl depletion produced by peritoneal dialysis (PD) against 0.15M $NaHCO_3$ (Cl-S) causes increased RR and diminished $TcH_2O/Cosm$ despite volume expansion by isoncotic albumin (Circ. Res. 44, 815, 1979). Since K depletion causes increased PRA and renin synthesis, and impaired Cl transport in the loop segment, we examined the effect of Cl-S on RR in 12 volume expanded KD and 10 control (CON) rats; both received a low salt diet for 1 week prior to study. In CON rats PRA rose from 18±3 ng/ml/hour (mean±SEM) before Cl-S to 57±3 after Cl-S ($p<0.001$). In KD rats PRA was 37±3 before Cl-S and was unchanged at 45±5 after Cl-S. Pre Cl-S PRA was higher than controls in KD rats ($p<0.001$) and post Cl-S PRA lower in KD than in control rats ($p<0.05$). BP and plasma Cl (77±3 vs. 81±2 mEq/L) were not different after Cl-S between KD and CON but FE_{Cl} was greater in KD (0.24±0.02 vs. 0.07±.006%, $p<0.001$) and U_{osm} less in KD {334±3 vs. 393±4 mOsm/kg ($p<0.01$)}. To determine if RR is responsive to other than macula densa stimuli in KD slow repeated arterial hemorrhage was performed in an additional 6 KD and 6 CON rats: PRA increased from 9±0.8 to 29±5 in CON ($p<0.01$) and from 14±2 to 34±10 in KD rats ($p<0.05$). We conclude that 1) KD is associated with impaired renin release in response to acute Cl depletion, despite increased initial PRA and, 2) renin response to hemorrhage was intact in KD. We suggest that elevated renin synthesis & release in KD are due to a defective macula densa Cl signal and that acute selective Cl depletion in these circumstances does not further increase macula densa mediated renin release.

DISTURBANCES OF CALCIUM (Ca) METABOLISM AND PARATHYROID (PTH) FUNCTION IN THE SPONTANEOUSLY HYPERTENSIVE RAT (SHR). David A. McCarron, Nam N. Yung,* Beth A. Ugoretz,* and Siegfried Krutzik.* Univ. of Oregon Hlth. Sci. Ctr., Div. of Nephrol., Portland, Oregon.

Emerging evidence suggests that PTH influences Ca's cardiovascular effects in both human and experimental hypertension. We characterized the basal serum ionized Ca (Ca++), PTH and UCaV of the SHR and its normotensive control, Wistar-Kyoto (WKY) rat, and evaluated the effect of chronic alterations of Ca intake. Repeated measures of serum Ca++, PTH, 24-hr urinary electrolyte excretion and systolic blood pressure (SBP) were made between 10-48 weeks of age. Equal numbers from each strain were fed 1 of 3 levels (% diet weight) of Ca (normal 0.5%, low 0.25%, high 4.0%) beginning at 10 weeks of age. Diet was otherwise identical. Ca++ was measured by ion-electrode, PTH by RIA and SBP by tail-cuff.

Irrespective of Ca intake, the SHR had lower serum Ca++ ($p<.001$) and higher PTH ($p<.001$) relative to WKY. Daily urinary Na and K excretions were similar for all rats. However, the SHR demonstrated greater UCaV ($p<.001$) throughout the study. The 4% Ca diet normalized serum Ca++ ($p<.001$) and significantly attenuated ($p<.001$) the SBP increase of the SHR. WKY BP was unaffected by level of Ca intake.

We conclude: 1) the SHR is a spontaneously hypocalcemic animal, with a previously unrecognized UCaV leak; 2) PTH levels are increased in the SHR, 3) these abnormalities of the SHR's Ca metabolism mimic recent observations in human hypertension, 4) Ca supplementation normalizes the SHR's serum Ca++ and attenuates its SBP increase.

THE ENDOGENOUS VASODILATORS BRADYKININ(BK) AND PROSTAGLANDIN E(PGE) IN RENOVASCULAR HYPERTENSION. J.Moore,* J.Gagnon, G.Sander,* P.Verma*, Dept. of Neph. and Clin. Phys., Walter Reed Army Medical Center and Institute of Research, Washington, D.C.

The relationships between the vasodilators BK and PGE and the vasoconstrictor activity of angiotensin II(AII) in renovascular hypertension(RH) induced by renal artery constriction were studied in anesthetized dogs. Mean arterial pressure(MAP), renal blood flow(RBF), plasma renin activity(PRA), renin secretory rate(RSR), arterial(a) and renal venous(rv) BK, PGE(rv), and urinary BK(UBK) were measured before RH(I), during RH(II), and during infusion of the dipeptidyl hydrolase inhibitor SQ20881 and RH(III). Results: (mean ± SE)

	I	II	III
MAP mmHg	142±6	154±5*	139±4*
RBF ml/min	288±27	239±38*	179±27*
PRA ng/ml	2.3±0.5	6.3±1.4*	12.1±3.0*
RSR mcg/ml/m	0.53±0.3	2.02±0.4*	1.59±0.2
BK(a) ng/ml	2.16±0.2	1.26±0.05*	5.28±0.7*
BK(rv) ng/ml	2.41±0.1	1.98±0.4	5.75±0.4*
UBK ng/ml/min	2.45±0.3	1.86±0.1	3.76±0.4*
PGE(rv) pg/ml	41±4.4	57±5.0*	113±15

*$p<0.025$ compared to preceding period.

During RH PRA, RSR, and PGE(rv) increased while BK (a and rv) and UBK did not. After SQ20881 PGE (rv) and PRA continued to rise. BK (a and rv) increased equally, while UBK also rose. These data suggest that a lack of increase in BK in response to vasoconstriction may contribute to RH. Moreover, the hypotensive response to SQ20881 may be mediated by several factors: decreased AII, increased PGE, and increased BK.

SPECIFIC DESENSITIZATION OF THE RENAL VASCULATURE TO ANGIOTENSIN II (AII) DESPITE CYCLO-OXYGENASE INHIBITION (COI). Leonard G. Meggs,* Richard W. Katzberg,* Peter W. Deleeuw,* and Norman K. Hollenberg. Harvard Medical School, Dept. of Medicine and Radiology, Boston, Massachusetts.

AII infusion sufficient to reduce renal blood flow (RBF) by over 50% leads to desensitization to AII in minutes: Prostaglandin (PG) release has been implicated because AII induces PG release; COI potentiates responses to AII as it prevents AII-induced PG release; and PGs modify smooth muscle responsiveness in many systems. To examine further relations between PGs and renal tachyphylaxis to AII we performed experiments in 10 anesthetized dogs. Subpressor bolus injections of AII and norepinephrine (NE) were injected into the renal artery to induce greater than 50% RBF reduction (electromagnetic flowmeter). A continuous AII infusion into the renal artery followed: within 5 minutes substantial recovery (65%) of RBF occurred; the response to AII bolus injection was lost but to NE sustained. A second group of dogs received indomethacin (5 mg/kg-i.v.) 30 minutes prior to study; recovery of renal blood flow during continuous AII infusion was much reduced (26%; $p<.02$). The response to the AII bolus, however, confirmed the influence of indomethacin on renal vascular responsiveness to AII, but specific desensitization of the renal vessels to AII occurred despite indomethacin. We conclude that different factors must underlie the poorly sustained response to AII and specific desensitization; the latter involves mechanisms other than prostaglandins.

MANAGEMENT OF HYPERTENSION IN DIABETES: EFFECTS OF K+ WASTING DIURETICS ON CARBOHYDRATE INTOLERANCE. Donna Myers, Robert Murphy,* Loretta Widman,* Arnall Patz,* and Gordon Walker. Johns Hopkins Hospital, Baltimore, Maryland.

Carbohydrate intolerance was studied in 46 diabetics on chronic diuretic therapy (+ DIUR) and 56 diabetics on no diuretic therapy (- DIUR). Determinations of the fasting blood sugar (fbs), serum potassium (serK+), urine potassium, blood pressure, insulin requirement and duration of diabetes (dmdurn) and hypertension were made. A majority of diabetics were on either furosemide (n=19) or hydrochlorothiazide (n=23), mean daily dose 64 mg and 50 mg, respectively, and the mean duration of hypertension was 10.4 yrs. The findings (mean±SEM) are summarized below:

		+ DIUR	- DIUR
n		46	56
serK+	(mEq/L)	4.18±.07	4.31±.05
fbs	(mg/dl)	222.3±12.1	222.2±12.6
insulin	(u/day)	38.8±4.2	32.8±3.1
dmdurn	(yrs)	16.5±1.2	17.2±1.1

On conventional diuretic therapy for hypertension there were no significant differences in serK+, fbs or insulin requirements in the two groups. Only 5 patients in the + DIUR group were on K+ supplements, mean dose 35 mEq/day. Because of a predominance of adult onset diabetics (aodm) vs juvenile diabetics (jodm) in the + DIUR group (91 vs 57%), the subgroup aodm/+ DIUR was compared to subgroups aodm/- DIUR and jodm/- DIUR. Again, there were no differences in serK+, fbs or insulin. We conclude that in diabetics on K+ wasting diuretics in whom the serK+ is normal there is no apparent adverse effect of diuretics on carbohydrate intolerance.

● EFFECTS OF LOW SODIUM INTAKE, DIURETICS AND PROPRANOLOL IN ISOLATED SYSTOLIC HYPERTENSION OF MIDDLE AGED. A.P. Niarchos, D.L. Weinstein* and J.H. Laragh. Hypertension Center, The New York Hospital-Cornell Medical Center, New York, N. Y.

Forty outpatients 35-59 years old with isolated systolic hypertension (ISH), that is BP >160/<90 mmHg and normal plasma renin activity (PRA) were treated with low sodium intake (low Na), with diuretics (D), with propranolol (P), or were left untreated (controls). There were 10 patients in each group with similar age. Low Na decreased ($P<0.05$) UNaV by 63±5% and increased ($P<0.005$) PRA by 121±41% and urinary aldosterone (UA) by 90±38%, but the systolic blood pressure (SBP) remained unchanged (from 170±3 to 167±2). Serum creatinine BUN, plasma K, uric acid and cholesterol did not change. D increased ($P<0.005$) UNaV by 151±48% and decreased the SBP by 20±2% (from 189±8 to 152±5), but D also increased ($P<0.05$) PRA by 380±80%, UA by 77±19%, uric acid by 42±8%, and cholesterol by 34±12%, and they decreased plasma K by 20±3%. P decreased ($P<0.05$) heart rate by 18±6%, the SBP by 14±4% (from 176±4 to 151±6), PRA by 72±22%, and UA by 13±6% (N.S.). The diastolic BP was not decreased by any of the treatments. The SBP did not change in the controls (from 172±6 to 167±5). Conclusions: 1) low Na does not decrease the SBP in ISH of middle aged because of other factors which maintain the SBP than Na intake in the range of 50-150 mEq; 2) the fact that D decreased the SBP in comparable patients suggests that D decrease SBP not only by volume and Na depletion alone; 3) since P decreases the SBP to the same level achieved with D but without the biochemical abnormalities of D which might be harmful in the susceptible patient, P should be preferable than D in the treatment of normal PRA ISH of middle aged.

● ANGIOTENSIN AND DIVALENT IONOPHORE STIMULATION OF PROSTAGLANDIN (PG) AND THROMBOXANE (Tx) SYNTHESIS BY RAT GLOMERULAR EPITHELIAL CELLS. Alice S. Petrulis*, Masamichi Aikawa* and Michael J. Dunn. Depts. of Medicine and Pathology, Case Western Reserve Univ. and Univ. Hosp., Cleveland, OH.

We have previously shown PG and Tx synthesis by isolated rat glomeruli incubated with arachidonic acid. In order to define the cellular origin of the PG and Tx we grew rat glomerular epithelial cells in culture and measured both angiotensin- and divalent ionophore- stimulated PG and Tx synthesis by these cells. Glomeruli from Sprague-Dawley rats were isolated by a sieving method and inoculated into culture dishes. Cellular outgrowth from these glomeruli, studied by scanning and transmission electron microscopy at 9 days, showed desmosomes and microvilli, consistent with epithelial morphology. Radioimmunoassay and radiometric thin layer chromatography were used to measure PG and Tx synthesis after stimulation with angiotensin II (ANG II) and the divalent cation ionophore A23187. The concentration-profile of endproducts for the two stimuli were different. ANG II stimulation of epithelial cells resulted in concentrations of PGE_2 >> $PGF_{2\alpha}$ > TxB_2 = 6-keto-$PGF_{1\alpha}$. The profile after A23187 was PGE_2 >> TxB_2 > $PGF_{2\alpha}$ >> 6-keto-$PGF_{1\alpha}$. Dose response curves for ANG II- and ANG III- stimulation of PGE_2 were similar and the Sar^1-Thr^8-ANG II analog inhibited both ANG II- and ANG III- stimulated PGE_2 synthesis. Our results demonstrate that: 1) glomerular epithelial cells synthesize PGs and Tx; 2) ANG II and ANG III increase predominantly PGE_2 synthesis, probably via the same ANG receptor; 3) A23187 enhances Tx synthesis as well as PGE_2 thereby differing from ANG II in the pattern of stimulation.

● MANAGEMENT OF EXTENSIVE BRANCH RENAL ARTERY DISEASE WITH EXTRACORPOREAL MICROVASCULAR RECONSTRUCTION AND AUTOTRANSPLANTATION. Andrew C. Novick, Cleveland Clinic Foundation, Cleveland, Ohio

Improved vascular reconstructive techniques now enable successful revascularization in patients with extensive branch renal artery disease who previously would have been considered inoperable or candidates for nephrectomy. From June 1977 to July 1980, 16 patients with intrarenal branch arterial lesions underwent extracorporeal microvascular reconstruction and autotransplantation. Renal revascularization was performed for treatment of renovascular hypertension in 12 patients and to prevent rupture of an arterial aneurysm in 4 patients. Renovascular disease was caused by fibrous dysplasia in 10 patients, saccular renal artery aneurysm in 4 patients, giant-cell arteritis in 1 patient and atherosclerosis in 1 patient. Four patients underwent operation for branch disease in a solitary kidney, 6 patients had renovascular disease in the contralateral unoperated kidney, and 6 patients had unilateral branch disease with a normal contralateral kidney. Preoperative studies included intravenous pyelography,isotope renography,renal arteriography and renal vein renin assays. Extracorporeal revascularization was performed with a branched autogenous vascular graft of the hypogastric artery,saphenous vein, or inferior epigastric artery. A total of 48 diseased renal artery branches were repaired (mean 3.0 per patient). There were no postoperative complications. All patients are currently normotensive including 3 patients who require antihypertensive therapy. Renal function has remained stable in all cases. Revascularization with preservation of renal parenchyma is possible in most patients with extensive branch arterial lesions.

PRESSOR RESPONSE TO NOREPINEPHRINE (NE) INFUSION IN NORMAL (NL) MAN: INFLUENCE OF IONIZED CALCIUM (Ca++) AND PTH. Laura I. Rankin, Friedrich C. Luft, and David A. McCarron. Divs. of Nephrol., Univ. of Oregon Hlth. Sci. Ctr., Portland, OR; Indiana Univ. Med. Ctr., Indianapolis, IN.

Previous studies indicate blood pressure (BP) response to NE is altered by physiological changes in Na+ and Ca++. PTH's role is unknown. We measured BP, Ca++, PTH and NE at mid-period during graded NE infusions in 8 NL in balance at 10 and 800 mEq Na+/d. After two control periods, NE was infused at 1, 2, 4, 8 and 16 µg/min for 30 min periods. Ca++ was determined by electrode, PTH by RIA and NE by radioenzymatic assay.

By ANOVA statistics, at 10 and 800 mEq Na+/d, mean BP (MBP) increased ($p<.05$) as NE was infused. NE and MBP were correlated at 10 ($r=0.76$) and 800 ($r=0.63$) mEq Na+/d; however, the slopes and intercepts differed ($p<.05$) Sensitivity to NE was increased at 800 mEq Na+/d. Ca++ was unchanged by NE at both levels of Na+ intake. With the initial NE (1 µg/min.) infusion, PTH increased ($p<.05$) at both 10 and 800 mEq Na+/d, but promptly returned to control levels with further increases in NE. PTH levels were similar at both levels of Na+ intake at all intervals. MBP was unrelated to variations in Ca++. However, for the NE infusions at 800 mEq Na+/d, individual PTH levels correlated with the MBP responses ($r=0.53$, $p<.001$). No such correlation was evident during the NE infusion at 10 mEq Na+/d.

We conclude: 1) Na+ loading increases sensitivity to NE infusions in NL humans; 2) endogenous PTH contributes to the enhanced sensitivity to NE at 800 mEq Na+/d, 3) this effect of PTH can be dissociated from that of Ca++.

OBESITY, HYPERTENSION, AND INCREASED VASCULAR RESPONSIVENESS TO NOREPINEPHRINE (NE) IN SODIUM-LOADED VENTROMEDIAL LESIONED RATS (VMH). Efrain Reisin,* Daniel H. Suarez,* and Edward D. Frohlich. Ochsner Medical Institutions, New Orleans, La.

Obesity and hypertension are linked in human beings. In order to study this effect in a more controlled fashion, obesity was produced experimentally in 9 Wistar rats by bilateral electrolytic lesions of the VMH; 9 sham age and sex matched rats served as controls. All rats were permitted ad libitum access to wet mash food and water (1.5% NaCl). Two months thereafter each rat had determination of intraarterial pressure (MAP), cardiac output (CO) reference method and organ flows (using 15μ ^{85}Sr or ^{141}Ce microspheres), plasma and total blood volumes (TBV) with RI^{125}SA, and responsiveness to increasing doses of NE (100 to 1000 ng/kg).

	BW g	MAP mm Hg	TBV ml/Kg	TPRI mmHg/ml/min/Kg
VMH	505±4***	133±4*	38±1***	0.613±0.03**
SHAM	415±16	120±4	54±2	0.477±0.03

Mean ±SE; *p<0.05; **p<0.005; ***p<0.001 by two-tailed t-test. BW:total body weight; TPRI:total peripheral resistance index.

Thus, VMH sodium-loaded rats had higher MAP and TPRI, contracted TBV, reduced distribution of CO blood flow to kidneys (19±1 vs 25±1%; p<0.001), and increased NE responsiveness (p<0.05). Therefore, this hypertension was more severe than our previous finding in VMH rats without NaCl load and similar to observations in patients with obesity-hypertension.

● **TRANSLUMINAL ANGIOPLASTY IN RENOVASCULAR DISEASE.** R.P. Russell, P.K. Whelton, S.L. Kaufman,* R.I. White,* G.M. Williams,* P.C. Walsh,* W.G. Walker, and K. Sova-Grim.* The Johns Hopkins Hospital, Baltimore, Maryland.

Over a two year period stenotic lesions in the renal arteries of 16 hypertensive patients (pts) with complex clinical presentations were selected for treatment by transluminal angioplasty (TA). Fifteen of the 16 pts had proven renovascular hypertension (RVH) while 1 patient was treated for preservation of renal function. Thirteen RVH pts had stenotic lesion(s) of their native renal arteries (fibromuscular dysplasia in 7 and arteriosclerosis in 6) while 2 had acquired lesions in arteries of transplanted kidneys. TA was technically successful in 13 and technically unsuccessful in 3 (19%) of the 16 patients. In 2 of the 3 pts with technically unsuccessful TA the balloon could not be passed across the area of stenosis while in the remaining pt adequate dilatation could not be accomplished. Only one serious complication (renal artery puncture) occurred in the 13 pts who underwent technically successful TA. The mean±SEM systolic blood pressure gradient across the stenotic lesion was reduced by TA from 123±19 mmHg before to 38±13 after (p<.001). In the 12 RVH pts whose lesions were successfully dilated by TA follow-up studies at 11±1 (SEM) months revealed 4 were cured, 5 were improved and 3 were unchanged.

Cure or improvement of hypertension in 60% (9 of 15 pts) of our patients with complex RVH compares favorably with other forms of therapy. These results suggest the importance of performing a controlled randomized trial of TA versus surgery in RVH.

CHANGES IN HEMODYNAMICS AND INTRA RENAL SODIUM HANDLING DURING CHRONIC CHLORTHALIDONE (CT) IN ESSENTIAL HYPERTENSION (EH). Jan C. Roos,* Evert J. Dorhout Mees,* Hendrik A. Koomans,* and Peter Boer* (intr. by Herbert G. Langford). Dept. of Nephrology, University Hospital, Utrecht, The Netherlands.

In order to investigate the mechanisms of blood pressure (BP) response, 8 patients with EH were studied before, on the 4th day, and after 3 months CT treatment (50 mg/day) during normal salt intake. Extracellular fluid volume (ECV) and plasma volume (PV) were measured as $^{82}Br^-$ and ^{131}J-albumin space, plasma renin activity (PRA), plasma aldosteron (PA), and BP response to saralasin (SR) by standard techniques. Free water clearance (C_{H_2O}) and GFR were studied during max. water diuresis from which fractional proximal sodium resorption (FRPNa) was calculated. After 4 days of CT treatment, while they were again in sodium balance, significant signs of volume depletion [including drop in mean arterial pressure (MAP) after saralasin: SR positive] were found in all patients, but BP changed variably. C_{H_2O}/GFR decreased 39% and FRPNa was proportionally increased. No correlations between the per cent changes (Δ) in these parameters were found at this time. After 3 months, however, despite decreased signs of volume depletion for the whole group, the following correlations were found: Δ MAP v. Δ ECV (r=-0.80), Δ MAP v. log PRA (r=+0.91), Δ MAP v. SR (r=-0.80), Δ MAP v. Δ C_{H_2O}/GFR (r=-0.82), Δ ECV v. Δ FRPNa (r=-0.78). It is concluded that the more BP decreases after prolonged CT treatment, the less degree of volume depletion remains. While the natriuretic effect of CT is first compensated for by an increased FRPNa induced by hypovolemia, the BP drop increases distal reabsorption thus enabling the kidney to maintain Na balance despite continous CT effect in the presence of less volume depletion.

DIFFERENT CLINICAL SETTINGS OF CLONIDINE WITHDRAWAL IN DIALYSIS PATIENTS. J.S. Sagar and S.J. Joshi, Deaconess Hosp. and V.A. Medical Center, St. Louis, Missouri

Clonidine (C) is a commonly used antihypertensive drug in the dialysis population because of good Blood Pressure (B.P.) control and lack of significant side effects. Major problem with C is post withdrawal hypertension for the first 72-96 hours with improvement on resumption of drug. Four clinical settings of hypertension are presented -

A: 44 year old male renal failure (ESRD) due to glomerulonephritis. High B.P. was major problem. Controlled partly with C and Inderal (I). Patient complained of recurrent post dialysis headaches with increase in B.P. improving about 6-8 hours after dialysis. Symptoms disappeared after discontinuation of C.

B: 66 y/o male ESRD due to high B.P. well controlled on C 0.5mg. QID, and I. Admitted to hospital for home training. Became progressively hypertensive over next 48 hours with diastolic in 120-140 range. Review of meds revealed that patient was being given 1/2 of 0.1mg. tab instead of 0.5mg. C. B.P. normalized after resumption of regular dose. I dose remained unchanged.

C: 42 y/o male admitted for elective TxP. High B.P. up to 150 diastolic in pre and post op period with high catecholamine levels. Controlled with Nitroprusside. B.P. controlled with native nephrectomy 6 months later

D: Patient ran out of meds at home and did not get refills. Admitted in hypertensive crisis. Improved within 72 hours after resumption of meds.

● THE NATURAL HISTORY OF ATHEROSCLEROTIC AND FIBROUS RENAL ARTERY DISEASE. M.J. Schreiber,* A.C.Novick, M.A. Pohl, Cleveland Clinic, Cleveland, Ohio.

From 1960-1979, 169 patients with 2 or more renal angiograms for renovascular disease (85 atherosclerosis (ASO), 75 fibrous, 9 ASO and fibrous) were reviewed in an attempt to characterize their progression. Of the 85 patients with ASO disease, (mean age 51 yrs.), the mean time interval between the initial and last angiogram was 35 mos. (range 1.5-172 mos.). Progression of renal artery ASO was observed in 37 patients (44%). 7/27 angiograms performed within 1 yr. demonstrated progression; 10/35 obtained during the 2nd year showed progression, 11/46 advanced from 3-5 years, and 9/35 after 5 yrs. Progression to complete occlusion was observed in 14 patients (16%), within a mean angiographic interval of 29 mos.(range 2.5-81 mos.). 75 patients with fibrous diease (66 medial fibroplasia, 3 intimal, 6 perimedial), mean age 41 yrs., had repeat renal angiograms from 2-137 mos. after the initial angiogram. In the 66 patients with medial fibroplasia, progression was observed in 22 patients (33%). In this group, the mean angiographic interval was 35 mos. (range 4-84 mos.). Medial fibroplasia advanced on 2 of 29 angiograms obtained in the 1st yr., progressed on 6 of 33 angiograms performed during the 2nd yr., while 10/45 noted progression at 3-5 yrs. and 4/29 after 5 yrs. There was no difference in the incidence of progression of medial fibroplasia in those individuals $<$ or $\geq$ 40 yrs. of age. No patient with medial fibroplasia progressed to total occlusion of the main renal artery. Of the 9 patients with both medial fibroplasia and ASO, 3 demonstrated progression of medial fibroplasia, while 2 showed advancing ASO.

RENAL HEMODYNAMICS IN YOUNG SPONTANEOUSLY HYPERTENSIVE RATS. Charles T. Stier* and William J. Arendshorst. Univ. of North Carolina School of Medicine, Depts. of Medicine and Physiology, Chapel Hill, NC.

Our previous studies have shown that glomerular filtration rate (GFR) and renal blood flow (RBF) are similar in conscious and anesthetized 12-week-old spontaneously hypertensive rats (SHR) with established hypertension and normotensive Wistar-Kyoto rats (WKY). The present clearance experiments were conducted to determine if renal hemodynamics differ in anesthetized 6-week old SHR (n=12) during the developmental phase of hypertension and WKY (n=11) under euvolemic conditions. Plasma protein concentration and hematocrit were maintained at presurgical levels by iv infusion of plasma from donor rats. The results shown below indicate that young SHR have a lower GFR, RBF and renal plasma flow (RPF) and a higher filtration fraction (FF) than age- and weight-matched WKY.

	SHR	WKY	P
Mean AP, mm Hg	107	83	<0.001
GFR, ml/(min·g KW)	1.0	1.2	<0.001
RPF, ml/(min·g KW)	3.1	4.3	<0.001
FF	0.32	0.28	<0.02
RBF, ml/(min·g KW)	5.4	7.5	<0.001
Left KW, g	0.45	0.44	
Body wt, g	88	94	

AP = arterial pressure. KW = kidney wt.

These differences may be related to an important role of the kidney in the pathogenesis of hypertension in this strain of genetically hypertensive rats.

EFFECTS OF CAPTOPRIL ON RENAL FUNCTION IN THE ISOLATED PERFUSED RAT KIDNEY. Ronald A. Sinicrope and Anton C. Schoolwerth. The Pennsylvania State University, Renal and Electrolyte Division, Hershey Pennsylvania.

Angiotensin converting enzyme inhibitor blocks the conversion of angiotensin I (AI) to angiotensin II (AII) and has been reported to increase cardiac output and glomerular filtration rate (GFR). To determine whether the increase in GFR represents a direct or indirect action on the kidney, the effects of captopril on renal function were studied using the isolated perfused rat kidney preparation. Kidneys were perfused according to the technique of Bowman using Krebs-Henseleit buffer containing 7.5% albumin and 5mM glucose. GFR was measured by the clearance of [^{3}H]-methoxyinulin. After a 30 min baseline period and at constant perfusion pressure, captopril was added to the recirculating perfusate in doses of 50,100,200,500 and 1000 µg/ml. Captopril produced a dose-dependent increase in GFR. Na^+ excretion and urine flow increased in parallel to the increase in GFR. FE_{Na} and FE_{H_2O} were unchanged. To provide further insight into the mechanism of the captopril effect, rats were either ECF volume expanded with saline or volume depleted with furosemide, and the kidneys, which presumably contained low and high renin contents, respectively, were perfused. The GFR increased following captopril addition to the perfusate of kidneys from volume contracted rats but not from volume expanded rats. These studies indicate that captopril increases GFR by a direct effect on the kidney. It is suggested that this effect is mediated by renal vasodilatation consequent to blocking the intrarenal conversion of AI to AII.

● HYPERKALEMIA AND HYPOALDOSTERONISM DURING CONVERTING ENZYME INHIBITION (CEI) IN AZOTEMIC PATIENTS. Stephen C. Textor*, Emmanuel L. Bravo*, Fetnat M. Fouad*, and Robert C. Tarazi*: (Intr. by P. Hall). Research Division, Cleveland Clinic Foundation, Cleveland, Ohio.

Inhibitors of angiotensin (Ang) converting enzyme have been associated with a fall in aldosterone excretion. To determine whether this effect of CEI represents a significant impairment of K^+ homeostasis, we studied 23 hypertensive patients treated with CEI alone in whom aldosterone excretion fell a mean of 63%. Creatinine clearance (GFR, ml/min), serum potassium (K^+, mEq/L), aldosterone excretion rate (AER, µg/d), plasma renin activity (PRA, ng/ml/hr) and aldosterone (PA, ng/dL) were measured before and during captopril for 4-7 days on 100 mEq Na, 80 mEq K^+ daily intake. Overall, there was no change in GFR (62 ± 6 to 56 ± 6), but K^+ rose (3.60 ± 0.14 to 4.37 ± 0.13, $p<0.001$) while AER fell (17 ± 2 to 6 ± 1) as did PA (39 ± 7 to 18 ± 2). PRA also rose (11 ± 3 to 27 ± 4, $p<0.001$). Final serum K^+ during CEI was inversely related to GFR ($r=-0.57$, $p<0.01$) with azotemic patients showing a greater rise in K^+ (*$p<0.001$) as shown below:

	(N)	AER	PA	K^+
GFR≤40	(6)	4.5 ± 0.8	18.4 ± 2.6	5.17 ± 0.16*
GFR>40	(17)	6.5 ± 1.0	17.4 ± 2.4	4.15 ± 0.13

Despite the rise in K^+, aldosterone failed to increase appropriately. Eight patients had an AER/K^+ ratio less than 1.1 indicating overt hypoaldosteronism. These results indicate a predominant role of Ang II in aldosterone regulation. The failure of AER to respond to K^+ elevation constitutes selective hypoaldosteronism during CEI. Furthermore, CEI in azotemic patients may produce a clinically important disturbance of K^+ homeostasis.

PROSTAGLANDIN E_2 (PGE_2) IN RENAL PAPILLA IN NaCl HYPERTENSION. L. Tobian, M. Johnson*, M. Ganguli*, J. Iwai*. U of Mn, Minneapolis & Brookhaven Lab, NY

Dahl S rats became hypertensive (159mmHg, n=21) after 4 weeks and more hypertensive (183mmHg, n=26) after 11 weeks of high (4%) NaCl diet. Dahl R rats remained normotensive (127mmHg, n=21) on this 4% diet. S and R rats on .3% NaCl diet were all normotensive. Isolated kidneys from S rats have reduced Na excretion. Intact S kidneys have reduced papilla plasma flow. PGE_2 concentration was measured in quick-frozen renal papillas, thus obtaining in vivo concentration. S rats had markedly reduced PGE_2 concentration. When normotensive on .3% NaCl, PGE_2 concentration averaged 42ng/100mg solids in R papillas vs 17 in S papillas, a 60% reduction ($p<.01$). After 4 weeks of 4% NaCl, R papillas averaged 80 ng while S papillas averaged 41, a 50% reduction ($p<.05$). After 11 weeks of 4% NaCl, R papillas averaged 78 ng while S papillas averaged 39, a 50% reduction ($p<.01$). Both S and R rats on 4% NaCl had twice the PGE_2 concentration of comparable S and R rats on .3% NaCl ($p<.05$). On any of the diets S rats were only half as high as R rats with regard to PGE_2. Inducing essential fatty acid deficiency in Sprague-Dawley rats reduces Na excretory rate and makes them susceptible to NaCl hypertension. Hence, the low PGE_2 in S papillas may partially explain the S rats' reduced Na excretion and great susceptibility to hypertension. Seventeen Sprague-Dawley rats given indomethacin (10mg/Kg) had an 18% lower papilla plasma flow than 18 comparable rats given vehicle (18.8 vs 23.0, $p<.05$). Seemingly, prostaglandins act as vasodilators for vessels supplying rat renal papilla. Thus, the low PGE_2 level in S papillas may well account for their markedly low papilla plasma flow, encouraging reduced Na excretion and hypertension in S rats.

● PARATHYROIDECTOMY (PTX) IN THE SPONTANEOUSLY HYPERTENSIVE RAT (SHR). Beth A. Ugoretz,* Nam N. Yung,* and David A. McCarron (intr. by Michael Hartnett). Univ. of Oregon Hlth. Sci. Ctr., Div. of Nephrol., Portland, Oregon.

To further define PTH's role in blood pressure (BP) regulation of experimental hypertension, we performed PTX in 8 SHR and 5 Wistar-Kyoto (WKY) rats (mean age 26 weeks). Four SHR and 6 WKY served as sham (S) controls. Systolic BP (SBP) was determined by tail-cuff method and Ca++ by ion-specific electrode. SBP (mmHg) and Ca++ (mEq/L) were measured pre-PTX, 6 days (d) post-PTX and then 14 days after calcium (Ca) repletion (21 days post-PTX) with a high Ca (4%) diet.

Mean SBP of the SHRs was significantly higher ($p<.001$) pre-PTX than in WKY. Following PTX, Ca++ declined ($p<.001$) in the SHR associated with a significant drop in SBP (186 vs. 158 mmHg; $p<.001$). SHR-S were unchanged. WKY-PTX experienced a similar fall in Ca++. However, mean SBP of WKY-PTX declined less (ΔSBP-SHR 37 mmHg vs. ΔSBP WKY 16 mmHg; $p<.05$) than that of SHR-PTX. Four percent Ca diet normalized the Ca++ of both SHR-PTX and WKY-PTX animals. Associated with this, mean SBP returned to pre-PTX levels ($p<.001$) for both SHR and WKY-PTX. Importantly, on the 4% Ca diet, mean SBP of the SHR-S and WKY-S also increased ($p<.01$). That increase, though, was less than that induced in the SHR-PTX ($p<.05$) and WKY-PTX ($p<.001$) rats.

In summary: 1) the BP of the SHR is more Ca++ dependent than the WKY's BP; 2) endogenous PTH has an influence on BP regulation, in part, distinct from that of Ca++; 3) intact, PTH function attenuates the pressor effect of Ca++ in both the SHR and the normotensive WKY animal.

PHASIC SECRETION OF RENIN. Randall H. Travis*, and Edmond S. Ricanati. Department of Medicine, Case Western Reserve University at Metropolitan General Hospital, Cleveland, Ohio.

In order to determine the temporal pattern of renin secretion (RS) in response to the stimulus of hemorrhage, 2 min. samples of arterial and left renal venous blood were collected continuously while left renal blood flow was monitored electromagnetically. RS was computed as the product of renal plasma flow and the arteriovenous difference for plasma renin concentrations. Measurements were made for 60 min. before and at least 54 min. after hemorrhage of 16 ml/Kg. completed in 2 min., in 5 anesthetized male mongrel dogs.

Control variables were stable. Hemorrhage was followed by a sustained reduction in mean arterial blood pressure (78.5% $\pm$ 1.0 of mean control) and in renal blood flow (87.3% $\pm$ 2.0 of mean control). An increase in RS began in every animal during the hemorrhage. This was transient reaching a peak at an average interval of 3.4 min. $\pm$ 0.75 and a nadir at an average interval of 9.0 min. $\pm$ 1.1, after initiation of hemorrhage. RS at the peak was 1,996.9% $\pm$ 977.8 of mean control and at the nadir was 87.6% $\pm$ 44.9 of mean control. After the initial transient increase there was a gradual irregular increase in RS. At 43 min. $\pm$ 1.3 after beginning of hemorrhage, a second surge of secretion began, during which the experiment was terminated.

These data demonstrate that the immediate changes in renin secretion in brisk hemorrhage are phasic. This characteristic must be taken into account when planning experiments in which RS is studied.

BLOOD PRESSURE AND RENAL RENIN SECRETORY PATTERNS BEFORE AND AFTER RENAL PERCUTANEOUS TRANLUMINAL ANGIOPLASTY (PTA). E. Darracott Vaughan, Jr., Thomas A. Sos,* Kenneth W. Sniderman,* Thomas G. Pickering,* David B. Case, Jean E. Sealey, and John H. Laragh. New York Hospital-Cornell University Medical Center, New York, N.Y.

Technical success after PTA occurred in 16 of 26 patients (62%). 14 of 16 have cure or improvement of blood pressure (B.P.). 6 patients had renal vein (RVR) and inferior vena cava (IVC) renin sampling before and after PTA (30"). Before PTA patients had an ipsilateral RVR concentration from 400% to 50% higher than IVC renin and absence of contralateral renin secretion (RVR-IVC = 0). Following PTA contralateral suppression persisted. The IVC level dropped in 5/6 cases indicating decreased renin secretion and the ipsilateral level dropped to about 50% above the IVC level. Three months after PTA 5 patients returned for repeat renin sampling. The IVC levels were 3.5 ng/ml/hr whereas they had been 10 ng/ml/min PTA. A 25% increment of both RVRS above IVC renin occurred indicating bilateral renin secretion. These findings show: (1) IVC (peripheral) renin level is an index of renin secretion, (2) contralateral renin suppression reverses after correction of renal artery stenosis and (3) a bilateral 25% increment of RVR above IVC renin reflects renin secretory behavior following reversal of renovascular hypertension and restoration of normal B.P.

MULTICENTER COMPARISON OF GUANABENZ AND HYDROCHLOROTHIAZIDE IN HYPERTENSION. B.R. Walker, M.W. Deitch, B.E. Schneider & J.A. Gold. Wyeth Laboratories, Philadelphia, Pa.

Guanabenz (G), a new nonsodium retaining, centrally active antiadrenergic antihypertensive drug, was compared to hydrochlorothiazide (H) in a randomized, blinded 3-month common protocol in 93 hypertensive outpatients (51G, 42H) at 4 sites. Pretreatment supine diastolic blood pressure (SDBP) was between 90-129mmHg with both groups comparable at baseline: 55% female, 56% white, mean age 50 yrs; 80% mild, 15% moderate, and 5% moderately severe hypertensives. Mean daily dose (mg): G-28, H-69. At 3 months, mean SDBP (mmHg) decrease was G:99 to 89 ($p<.01$), H:100 to 88 ($p<.01$). Clinically significant individual SDBP decreases occurred in 23/29 (79%) G and 31/39 (79%) H. Mean G weight (lbs) increased by 0.2 and decreased in H by 4.3 ($p<.01$). Mean supine pulse (beats/min) decreased in G by 4.9 ($p<.01$) and in H by 1. Dropouts from nonresponse were similar in both groups with adverse effects slightly higher in G (mainly dry mouth & sedation). Impotence or postural symptoms of hypotension were not reported by either group. Metabolic abnormalities were limited to H (elevated CO_2, uric acid, BUN, creatinine; decreased K, Cl). Results suggest that G may be an effective alternative drug to H for initial, sole therapy of hypertension in view of its efficacy, lack of sodium retention or metabolic abnormalities.

RACIAL DIFFERENCES DURING CHRONIC PRAZOSIN(PZN) THERAPY OF HYPERTENSION. SE Warren, DT O'Connor, J Cervenka* VA Med Ctr & U of Cal, San Diego, CA.

PZN may affect the renal circulation and volume homeostasis differently in black(BK)vs. white(WH) patients. We studied the following parameters in 11 BK and 11 WH essential hypertensives on placebo and during chronic PZN therapy: Mean Arterial Pressure(MAP in mmHg);Clearance of Creatinine(GFR),PAH clearance(PAH),Renal Blood Flow(RBF)(all in ml/min); Renal Vascular Resistance(RVR in dyne.sec.cm^{-5}); Blood Volume(BV in ml);Plasma Renin Activity(PRA in ng AI/ml/hr);and Urinary Kallikrein(a renal vasodilator system, UKa in EU/24h). The median PZN dose for both groups was 6mg/day(range 3-15mg). Results appear as mean ± SEM; p = paired or unpaired t-test values.

	Black			White		
	placebo	PZN	p	placebo	PZN	p
MAP	125±4*	111±4*	<.01	115±3	101±3	<.01
GFR	111±7	113±6	NS	114±9	106±6	NS
PAH	725±81	730±62	NS	627±50	638±48	NS
RBF	1286±147	1296±117	NS	1049±75	1118±90	NS
RVR	9129±926	7366±650	<.01	9090±827	7581±503	<.01
BV	5206±518	6805±254†	<.01	6120±232	5967±220	NS
PRA	2.72±0.9	0.43±.16	<.01	1.52±.37	2.10±.79*	NS
UKa	5.6±2.8	4.9±1.5	NS	9.6±2.1†	11.1±2.9†	NS

†,* = BK>WH or WH>BK; † = $p<.05$, * = $p<.01$

We conclude: 1) PZN effectively lowers MAP in both BK and WH hypertensives. 2) On PZN, renal perfusion is preserved with reduced RVR in both groups. 3) BK patients show a higher BV and lower PRA than WH hypertensives patients during chronic PZN therapy. 4) Because BV is increased and UKa decreased in BK patients, the importance of concurrent diuretic therapy in BK hypertensives treated with prazosin is emphasized.

DOPAMINE β-HYDROXYLASE(DBH)MEASUREMENTS AND MYOCARDIAL FUNCTION. SE Warren, DT O'Connor, G Levine* VA Med Ctr & U of Cal., San Diego, CA.

Low plasma DBH activity has been reported in patients with congestive heart failure (CHF) suggesting that DBH assay might be a noninvasive index of myocardial function. We measured supine DBH activity in 21 consecutive adult patients undergoing cardiac catheterization(Cath) for a variety of conditions, including 12 with CHF; and in 24 normal controls. Cardiac index (CI) was measured, and expressed in units of L/min/m^2. Cath patients were divided into those with CHF i.e., CI<2.5 L/min/m^2; and those without CHF i.e., CI>2.5 L/min/m^2. DBH values (in IU/L) were then correlated with measures of CI at Cath. Results as mean ± SEM; p=level of significance:

	CHF(n=12)	No CHF(n=9)	p value
CI	2.0±0.1	3.0±0.1	<0.01
DBH	20.6±4.0	46.8±7.4	<0.01

Normal controls had plasma DBH of 41.5±4.2 IU/L, higher ($p<0.01$) than CHF patients, but no different ($p>0.1$,NS) from non CHF patients. DBH was correlated with CI: $r=0.40$, $p=0.08$, $n=21$.

We conclude: 1) plasma DBH activity is significantly reduced in patients with depressed cardiac function; 2) while a low DBH value may be supportive of a diagnosis of reduced cardiac function, the correlation of DBH with cardiac index measurements over a wide range of hemodynamic profiles (CI 1.5-3.6 L/min/m^2) is too low to be of high individual predictive value.

CATECHOLAMINES, SODIUM AND RENIN IN UNILATERAL RENAL HYPERTENSION IN MAN. P. Weidmann, H. Schiffl,* W.H. Ziegler,* Z. Glück,* A. Meier,* and G. Keusch.* Medizinische Poliklinik, University of Berne, Switzerland.

The relative roles of plasma or urinary norepinephrine (NE) and epinephrine (E), exchangeable sodium, blood volume, and plasma renin (PRA) or aldosterone in the pathogenesis of unilateral renal hypertension was evaluated. Ninety-nine normal subjects and 33 age-matched untreated hypertensive patients with unilateral renal parenchymal disease (RPD, N=18) or renal artery stenosis (RAS, N=15) were compared. Measurements were repeated following operative treatment in 23 patients. Plasma and urinary NE or E, exchangeable sodium and blood volume were comparable between normal and untreated subjects with RPD or RAS. Both patient-groups had increased blood pressure and supine PRA ($P<0.001$); these abnormalities were milder in RPD. Plasma aldosterone and upright PRA were significantly elevated ($P<0.05$) in RAS only. Operative treatment of RPD and RAS caused decreases in blood pressure (-18 and -28%) and PRA; they correlated significantly in RPD ($r = 0.56$; $P<0.05$). In RPD and RAS, exchangeable sodium, blood volume, and NE or E values remained unchanged following operation, except for mildly increased upright PNE in RAS. These observations suggest that the sympathetic system plays no major role in unilateral renal hypertension in man. However, the "normal" body sodium-volume state in RPD or RAS may be inappropriate relative to co-existing hypertension. In addition to its established role in RAS, mild activation of the renin-angiotensin-system may be also important for the pathogenesis of hypertension caused by unilateral RPD.

RELEASE OF RENIN AND PROSTAGLANDINS FROM THE DOG KIDNEY DURING HYPERTONIC SALINE INFUSION. Christopher S. Wilcox, Shirley Roddis*, W. Stanley Peart*, David Gordon* and Graham P. Lewis*. Med. Unit, St Mary's Hospital Med. Sch., London & Dept. of Pharmacol., Royal Coll. of Surgeons, London, UK.

Infusion of hypertonic NaCl provokes renal vasoconstriction and natriuresis (Nashat, Tappin and Wilcox, J. Physiol. 256, 731, 1976). We have investigated whether these changes are accompanied by release of renin or prostaglandins from the kidney. Renin concentrations were estimated in arterial and renal venous plasma and renal lymph (12 experiments) by radioimmunoassay of AI formed from excess homologous substrate, (Wilcox, J. Physiol. 284, 203, 1978). Prostaglandin (PG) concentrations were estimated in urine (5 experiments) by radioimmunoassay of PGE_2, PGF_2alpha, 6-keto-PGF_1alpha (metabolite of prostacyclin) and thromboxane B_2 (metabolite of thromboxane A_2). Measurements were made 30-45 minutes after increasing the NaCl concentration of an intra-renal-arterial infusion of saline from 0.154M to 1.232M. This increased the sodium concentration in renal arterial plasma by 22±4 mmole l^{-1}. There were no changes in BP but significant falls in renal blood flow of 20±9% ($p < 0.01$). The infusions did not elicit release of renin into the blood or the lymph. However, there were significant ($p < 0.02$) increases in the renal excretion of all the four prostaglandins measured. We conclude that the infusion of hypertonic saline does not elicit release of renin into the renal interstitium. However, there appears to be an increase in arachidonic acid metabolism to prostaglandins which could participate in the vasoconstriction and natriuresis that occur.

DEFECT IN CONVERSION OF INACTIVE RENIN (IR) TO ACTIVE RENIN (AR) IN DIABETIC SUBJECTS WITH NEPHROPATHY (DN) AND HYPERKALEMIA (HK). P.G. Zager, W.A. Hsueh*, J.A. Luetscher*, D. O'Conner, S. Warren*, Stanford Univ., Stanford,Ca., USCD Med Ctr, San Diego, Ca.

Renin activation was studied in 5 diabetics (D) with DN and HK. Levels of plasma renin activity (PRA), AR, IR and aldosterone were determined in plasma samples obtained both at 0800 supine and 1200 upright before and after dietary sodium restriction. In sodium replete state PRA and AR were normal (N). PRA and AR were 0.8 ± 0.2 and 4.4 ± 1.2 ng/ml/hr respectively at 0800, and increased after standing in only 1 D. Supine and upright values for IR were 6 fold above N. PA was 6.2 ± 1.4 and 14.0 ± 1.5 ng/dl at 0800 and 1200.

Dietary sodium restriction produced a cumulative sodium loss of 258 ± 32 mEq. The responses of PRA and AR to sodium depletion and upright posture were blunted. At 0800 levels of PRA and AR were 1.2 ± 0.4 and 8.0 ± 2.0 ng/ml/hr. At 1200 PRA and AR were 2.6 ± 0.6 and 12.6 ± 4.6 ng/ml/hr. PA was 14.2 ± 1.0 and 30.8 ng/dl at 0800 and 1200. Levels of IR at 0800 and 1200, however, were 6 fold greater than N. Urinary kallikrein in the sodium replete state was below N and failed to increase during sodium depletion. PA response to ACTH was N in 4 D.

The above data indicate that in D,IR is more sensitive than AR to changes in sodium balance. The inability to raise plasma levels of AR may be due to impaired conversion of IR to AR resulting in renal release of IR rather than AR. Deficiency of urinary kallikrein may contribute to defective renin activation.

Immunology and Pathology

A CLINICOPATHOLOGICAL ANALYSIS OF 12 PATIENTS WITH TYPE III MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN). Kenneth Abreo* and A. Vishnu Moorthy, Dept. of Medicine & Pathology, University of Wisc., Renal Section, V.A. Hospital, Madison, Wisconsin. (Introduced by Arvin B. Weinstein).

Besides the two usually described varieties of MPGN: Type I (with glomerular subendothelial deposits) and Type II (dense deposit disease) Burkholder et al. have described a third variant with extensive subepithelial glomerular dense deposits on electron microscopy (EM) (Lab. Invest. 23:459, 1970).

We studied 12 patients with Type III MPGN. 8 were male and 4 were female. Their mean age was 30.9 yrs (13-50 yrs). Six patients presented with nephrotic proteinuria and 6 with lesser proteinuria. 11 had microscopic hematuria at onset, 7 had hypertension, 5 had low C_3 levels. All had normal C_4 levels. Initially 10 patients had a serum Cr < 2 mg/dl. There were 16 renal biopsies. All showed glomerular lobularity, hypercellularity, peripheral capillary wall thickening and splitting of the basement membrane on light microscopy. On immunofluorescence only C_3 was seen in glomeruli in 7. Others had IgG & C_3. On EM all had extensive glomerular subepithelial deposits. Ten patients were followed for up to 12 yrs (mean 6.2 yrs). In 4 serum Cr has remained below 2 mg/dl at 3, 6, 9 & 12 yrs. In 2 serum Cr is between 2-3 mg/dl at 7 & 8 yrs. 1 has a serum Cr of 3.9 at 1-1/2 yrs while 3 developed end stage renal failure after 3, 5 and 8 yrs. Hypertension, proteinuria and/or hematuria persisted throughout their follow-up as was hypocomplementemia. Many different forms of therapy did not appear to have an effect on their course.

Type III MPGN is a variant of MPGN with distinctive EM findings and a fairly benign course.

ONE GLOMERULAR DISEASE DOES NOT EXCLUDE ANOTHER. Tatiana T. Antonovych, and Sharda G. Sabnis.* Armed Forces Institute of Pathology, Division of Nephropathology, Washington, D.C. and American Registry of Pathology, Registry of Nephropathology.

A variety of renal diseases are known to produce similar clinical symptoms, often making the differential diagnosis difficult. When two diseases co-exist, the problem is multiplied. We would like to illustrate four such cases. The first case, diabetic nephropathy and acute post infectious glomerulonephritis; the second, diabetic nephropathy and membranous glomerulonephritis; the third, hereditary nephropathy with dense deposit disease; and the fourth, hereditary nephropathy and lupus nephritis. The illustrations (light and electron microscopy) will be accompanied by clinical data.

ONTOGENY OF PROXIMAL TUBULAR ANTIGEN (FxlA) IN METANEPHRIC ORGAN CULTURE.* E.D. Avner*, D.B. Villee*, E.E. Schneeberger and W.E. Grupe, Departments of Pediatrics and Pathology, Harvard Medical School, Boston, Massachusetts

The presence of FxlA was determined in intact fetal mouse kidneys and metanephric organ explants by indirect immunofluorescence using acid eluate of glomeruli from rats with active Heymann nephritis. FxlA developed in vivo in a typical periluminal location after 16 ± 0.3 days' gestation. Metanephros explanted into organ culture after 14 ± 0.3 days' gestation was harvested after 3-12 days incubation in vitro. Explants were maintained in chemically defined medium supplemented with 10% fetal calf serum. By the 3rd day in culture, glomeruli and tubules had developed from S-shaped structures amid undifferentiated mesenchyme. Columnar proximal tubular cells had become laterally attached, and radially oriented with irregular short brush borders. The latter had elongated by day 4 to surround central lumens filled with debris. By day 5, (19 ± 0.3 days post-conception) characteristic periluminal immunofluorescence was apparent concomitantly with increasing numbers of apical vacuoles, vesicles and membrane limited cytoplasmic inclusion bodies. At the time FxlA developed in culture, glomerular differentiation had proceeded without vascularization creating an epithelial tuft of differentiating podocytes complete with slit diaphragms encircling islands of basement membrane. No endothelial structures were seen in the glomeruli examined.

Therefore, FxlA develops in situ in organ culture without evidence of vascular supply, blood flow or ultrafiltration and can serve as a specific proximal tubular marker during metanephric development in vivo or in vitro.

IN VITRO AND IN VIVO REACTIVITY OF A MONOCLONAL ANTIBODY TO RAT FxlA. Atul K. Bhan,* Diane Crawford,* Eveline E. Schneeberger,* Alfred B. Collins,* and Robert T. McCluskey. Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

A monoclonal antibody against rat FxlA was made by somatic cell hybridization of spleen cells of a BALB/c mouse immunized with rat FxlA in complete Freunds adjuvant with P3-NSI-1-Ag4-1 myeloma cells by the method of Kohler and Milstein (Nature 256:495, 1975). Hybridoma cultures containing antibodies reactive with brush border regions of proximal tubules in frozen sections of normal Lewis rat kidneys, as detected by indirect immunofluorescence, were selected and subcloned twice by a limiting dilution method. One of the clones was injected intraperitoneally into BALB/c mice primed with pristane (Aldrich Chemical Co., Milwaukee, WI). The ascitic fluid was tested by indirect immunofluorescence for its reactivity against brush border antigen in Lewis rat kidneys. All proximal tubules showed brush border staining; however, some tubules showed intense staining, whereas others were less intensely stained. There was no glomerular staining. Intravenous injections of varying doses of antibody into Lewis rats did not result in granular deposits in glomeruli, as judged by indirect immunofluorescence or by electron microscopy, within a 2 to 5 day period of observation. The findings obtained so far indicate that the monoclonal antibody recognizes an antigen that is present in varying amounts in brush border regions of proximal tubules, but provides no evidence that the antigen is present in glomeruli.

EVIDENCE FOR HETEROGENEITY OF RETICULOENDOTHELIAL SYSTEM (RES) FUNCTION IN MICE PRETREATED WITH POLYNUCLEOTIDES (PN). U. Barcelli*, R. Rademacher*, and B. S. Ooi. Dept. of Med., Univ. of Cincinnati Medical Center, Cincinnati, Ohio.

Studies have demonstrated that the RES modulates the deposition of immune complexes (IC) in the kidney. Because of previous reports that PN enhance macrophage phagocytosis, we investigated the in vivo clearance of IC in mice pretreated by these substances. A bolus of BSA-^{125}I-anti-BSA containing 3 mg ^{125}I-anti-BSA was given to groups of mice (8 each): controls and mice pretreated with the polynucleotides poly A:poly U (50 µg) and poly I:poly C (50 µg and 100 µg). The mice were sacrificed at 3 hours after injection of IC. Blood, liver and spleen were counted for radioactivity and glomeruli assessed by immunofluorescence (IF). The results showed:

	Control	Poly AU	Poly IC (50 µg)	Poly IC (100 µg)
Blood (µg/ml)	453	456	511†	568†
Liver (µg/org)	616	543†	530†	501†
Spleen (µg/org)	11.8	18†	20.5†	19.0†
Kidney (IF)	+++	+++	+++	+++

† = Statistically significant

The results showed that in the PN treated mice, there was enhanced splenic uptake of IC, but diminished liver uptake of IC. Blood clearance was diminished in the poly I:poly C treated mice, reflecting impaired liver uptake. No differences in glomerular localization of IC were seen. The study demonstrates that the RES behaves heterogeneously in response to PN challenge and underlines the critical role of the liver in modulating blood levels of IC.

DISTINCTIVE RENAL VASCULAR LESIONS IN NORMOTENSIVE PATIENTS WITH LUPUS NEPHRITIS (LN) D.B. Bhathena, S.D. Migdal, B.J. Sobel, and F.D. McDonald. Dept. of Pathology & Med., Wayne State Univ. School of Med. and Hutzel Hospital, Detroit, MI

Noncapillary renal vascular lesions resulting from systemic lupus erythematosis are reported to be exceedingly rare in patients with LN. Most vascular lesions are said to result from concomitant hypertension. The majority of previous reports are based on autopsy material and none of the tissue has been completely studied by correlated light (LM), immunofluorescence (IF) and electron microscopy (EM). We have reviewed biopsies performed in 12 pts. with LN over the last 12 months. The mean pt. age at biopsy was 28. Striking vascular lesions were found in six of these patients studied by LM, IF, and EM. These were not associated with any one type of glomerular lesion. Only 1 of these pts. was hypertensive prior to biopsy. 5 pts. had non inflammatory microangiopathy involving afferent arterioles and distal interlobular arteries. The lesions were characterized by strongly PAS positive deposits of immunoglobulins (IgG, IgA, IgM, C_3) in the lumens and walls and distinctive destruction of the vascular architecture. These lesions resembled those of malignant hypertension and the thrombotic microangiopathies and resulted in luminal narrowing and occlusion. The 6th pt. displayed necrotizing arteritis of the polyarteritis type involving larger arteries.

Except for the increased incidence of microangiopathic hemolysis in pts. with these vascular lesions, they could not be distinguished clinically from those without them. 4 pts. subsequently developed hypertension.

These data suggest that distinct noncapillary vascular lesions occur in young normotensive pts. with LN. The prognostic significance of these lesions remains to be determined.

EVIDENCE OF IMMUNOREGULATORY ABNORMALITIES IN PATIENTS WITH HENOCH SCHONLEIN SYNDROME (HSS) NEPHRITIS. M.Beale,G.Nash* and R.MacDermott* (intr. by B. Cole). Wash.U.Sch. of Med., St. Louis, MO.

Although the etiology of HSS is uncertain, an immune pathogenesis is suspected. IgA and IgG, and less commonly, IgM have been demonstrated in the skin, kidneys, and circulating immune complexes of affected patients. We evaluated the Ig synthesizing capacity and immunoregulatory function of peripheral blood lymphocytes (PBL) from 4 pediatric patients with HSS nephritis 2,14,40, and 91 months following the onset of their disease. The mean spontaneous and pokeweed mitogen (PWM) induced Ig synthetic rates were:

	N	IgM (ng/ml)		IgG (ng/ml)		IgA (ng/ml)	
		unstim	PWM	unstim	PWM	unstim	PWM
Control	4	209	3545	221	3458	227	1509
HSS	4	419	107	2002	352	2778	470

In co-culture experiments, control MNC inhibited spontaneous IgG and IgA synthesis of patient PBL by a mean of 57% suggesting that patient PBL have the capability to respond to normal suppressor influences. Conversely, patient PBL profoundly inhibited PWM stimulated IgM, IgG, and IgA synthesis by control PBL indicating a marked enhancement of PWM induced suppression. Patient T cells failed to support Ig synthesis by control B cells in the presence of PWM while co-cultures between patient B cells and control T cells exhibited normal synthetic patterns. These studies suggest that IgG and IgA synthesis are increased during acute and convalescent stages of HSS.Moreover,the patients appear to be lacking cells capable of inhibiting spontaneous Ig synthesis. The observed increase in PWM related suppressor activity may represent a compensatory response to excessive Ig production.

CYCLOPHOSPHAMIDE EFFECTS ON EXPERIMENTAL AUTOLOGOUS IMMUNE COMPLEX (AIC) GLOMERULONEPHRITIS (GN). D. C. Cattran,* D. Man, W. Chodirker, University of Toronto and Western Ontario. Canada.

Single shot AIC GN was induced in male Wistar rats using 3 mg. of human renal tubular epithelial antigen (Ag). One group received only Ag(C),others received Ag plus cyclophosphamide (CY) 10, 125 or 300 mg. 2 days before (DB),day of antigen (DO) and 2 and 7 days after (DA) Ag. (8 rats each group). The rats' sera was monitored for: (i)circulating antibody (Ab) by indirect immunofluorescence (IIF) and hemagglutination (HA). (ii) free Ag (immunodiffusion against rabbit antibody to Ag. (iii)circulating immune complexes (CIC)(C1q solid phase binding assay). As well, periodic renal biopsies were taken for light, IF and electron microscopy.

No free Ag was found in any group. Free Ab was found by 20 days in C and all 10 mg.CY groups with subsequent IC seen in a granular pattern on GBM and around tubules by day 30. High Ab titres persisted, granularity ↑ and proteinuria was noted by day 90 to 120. The 300 CY group did not develop a significant Ab titre until >50 days and renal tissue showed absence of IC deposits on GBM by IF and EM. The 125 CY group was variable. Circulating IC's were detected in low titre only and showed no parallel to renal pathology (positive control was heat aggregated rat IgG, which showed >95% binding). The low titres of CIC and the presence of high free Ab titres suggests the model progresses in a state of antibody excess. The disease is aborted by high dose CY even given 7 DA the inciting antigen and this effect more closely parallels the change in Ab titre than it does on CIC's.

● INCREASED SPONTANEOUS IMMUNOGLOBULIN (Ig) SYNTHESIS IN CHILDREN WITH MINIMAL CHANGE NEPHROTIC SYNDROME (MCNS), FOCAL GLOMERULOSCLEROSIS (FGS), AND SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). M.Beale,G.Nash*, and R. MacDermott*. Wash.U.Sch. of Med., St.Louis, MO.

Reports of circulating immune complexes (CIC) in patients with MCNS and FGS have raised new questions concerning the role of the humoral immune system in the pathogenesis of these disorders. To assess potential disturbances in humoral function we evaluated the spontaneous and pokeweed mitogen (PWM) induced Ig synthesizing capacity of peripheral blood lymphocytes (PBL) from untreated patients with MCNS in relapse (N=10), MCNS in remission (N=8) and FGS (N=3). Similar studies were performed in 8 patients with SLE and 18 healthy controls for comparison. The mean Ig synthetic rates were:

	IgM (ng/ml)		IgG (ng/ml)		IgA (ng/ml)	
	unstim	PWM	unstim	PWM	unstim	PWM
Control	136	1490	269	2442	229	1162
MCNS-relapse	879	871	1977	1732	4020	2028
FGS	577	3209	618	2120	2212	2069
SLE	646	159	1987	508	3570	713

Ig synthesis remained abnormal in MCNS patients who had been in remission < 6 months; patients in longer remission exhibited normal synthetic patterns. The high levels of spontaneous Ig synthesis in general and IgA synthesis and secretion in particular, plus the resistance to further augmentation by PWM suggest that PBL from patients with MCNS and FGS are polyclonally activated *in vivo*. Moreover, the degree of activation is similar to that observed in PBL from SLE patients. The detection of CIC in MCNS and FGS patients may be a reflection of heightened Ig synthesis against as yet undefined antigens.

● SELECTIVE DEPOSITION OF IgA_1 IN IgA NEPHROPATHY, ANAPHYLACTOID PURPURA NEPHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS. M.E. Conley,* M.D. Cooper* and A.F. Michael, Univ. of Minnesota and Alabama.

The IgA in mucous secretions differs from serum IgA in that it is made up of approximately equal amounts of IgA_1 and IgA_2 whereas serum IgA is 80-90% IgA_1 and in addition is predominantly dimeric rather than monomeric. In order to characterize the IgA deposits found in glomeruli of patients with nephritis associated with IgA nephropathy (10 pts.), anaphylactoid purpura (11 pts.), and lupus erythematosus (9 pts.), renal biopsies were stained by immunofluorescence techniques with monoclonal antibodies to the IgA subclasses (IgA_1 and IgA_2) and with antiserum to J chain. The mesangium and/or peripheral capillary were brightly stained for IgA_1 and were negative for IgA_2 in all 3 diseases. In contrast, the protein in tubular casts contained both IgA_1 and IgA_2. The specificity of the reagents was verified by reactivity of the monoclonal antibodies with the appropriate IgA subclass by ELISA, radioimmunoassay, and immunofluorescent staining of plasma cells from patients with multiple myeloma. In addition, the reagents identified IgA_1 and IgA_2 plasma cells in the submucosa of small bowel biopsies. Both kappa and lambda light chains were present in glomeruli indicating that the IgA deposits were not monoclonal. The intensity of J chain staining correlated with the intensity of IgM and not IgA; tissue which stained brightly for IgA and negatively for IgM was negative for J chain indicating the absence of polymeric IgA. These results indicate that glomerular IgA deposits in these disorders consist predominantly of monomers of IgA_1 of polyclonal origin similar to serum and not secretory IgA.

LONG TERM PATHOLOGIC EFFECTS OF CIS-DIAMMINEDICHLOROPLATINUM (CP). Dennis C. Dobyan, Don Hill,* Theresa Lewis,* and Ruth Ellen Bulger. Univ. of Texas Health Science Center, Houston, Texas.

A single IP injection of CP causes acute tubular necrosis of the S_3 segment of the proximal tubule (PT) located in the outer stripe of the medulla. One week after the administration of the drug both tubular injury and tubular regeneration can still be observed. To further examine the extent of renal injury, Fisher 344 rats were given a single IP injection of CP (6 mg/kg B. Wt.) and the morphologic changes were examined by LM, SEM, and TEM at 2,3 & 4 weeks and 6 months after drug treatment. After 2 weeks, the S_3 segments of the PTs in the outer stripe were widely dilated and were lined by low-lying epithelial cells with scattered apical microvilli. These changes appeared to be progressive and by 1 month the tubules were seen as cystic dilatations lined by low epithelial cells. Florid, regenerative, nuclear atypia could be seen in these low-lying cells as well as in cells which were not as severely damaged. Mononuclear cells could be seen on the luminal surface of these dilated tubules. Striking changes were still apparent 6 months after drug treatment. Large multiple cysts up to 2.8 mm in diameter were seen in the outer stripe extending into the cortex. These cysts were lined by a simple squamous epithelium possessing microvilli and microplicae. Many of the tubules at the periphery of the cysts were collapsed. At all time periods examined there was extensive interstitial fibrosis, atrophic tubules and casts in the distal segments of the nephron. In 2 animals there were small nodular foci of abnormal epithelial cells. These results suggest that CP induces a long term injury which results in the formation of large cysts.

● MODULATION OF AUTOLOGOUS IMMUNE COMPLEX NEPHRITIS (AIC) BY PRE-IMMUNIZATION WITH AUTOANTIBODIES OR SENSITIZED CELLS. T.H. Ebert, R.T. McCluskey, A.B. Collins,* and R.B. Colvin* Dept. of Path., Mass. Gen. Hosp., Boston, MA

Immunization of rats with FxlA induces autoantibodies to the brush border (BB) and a chronic glomerulonephritis (AIC, Heymann nephritis). Because anti-idiotype antisera can modulate other autoimmune diseases, we hypothesized that pre-immunization with the relevant autoantibody might alter AIC. In two experiments we pre-immunized Lewis rats with anti-BB from AIC kidney eluates, rat IgG, or normal (N) kidney eluate on protein A in IFA. Animals were immunized 10 days later with 3mg FxlA in CFA and pertussis adjuvant and serum anti-BB titer and urinary protein were monitored for 10 weeks. Our results were:

Preimmunization:	AIC eluate	Eluate/IgG
GBM deposits >1+	1/12	8/12 $p \leq 0.005$
Anti-BB titer >1:100	2/12	9/11 $p < .003$
Proteinuria >50mg/d	0/6	3/5 $p = 0.06$

The data indicate that pre-immunization with anti-BB antibodies inhibited AIC and the production of anti-BB antibody. To determine whether a similar response could be evoked with sensitized cells, we pre-immunized animals with lethally irradiated spleen and lymph node cells from FxlA/CFA or CFA-immunized animals. This treatment did not inhibit, and may have accelerated, the development of AIC.

Although we do not yet have proof, by analogy with other well-characterized immunoregulatory models, we postulate that pre-immunization with autoantibodies promptes an anti-idiotype response that can modulate the course of this chronic autoimmune glomerulonephritis.

● T-CELL MEDIATED IMMUNITY (CMI) TO HAPTEN CONJUGATED RENAL CELLS. Douglass T. Domoto. Department of Medicine, University of Chicago, Chicago, Illinois.

The ability of fluoresceinated kidney cells to induce or elicit T-lymphocyte mediated immune responses in vivo was examined. Fluorescein isothiocyanate (FITC) acts as a hapten when conjugated to syngeneic spleen cells (FITC-SC) and induces or elicits a T-cell response in mice. FITC also produces contact sensitization (CS), another T-cell reaction. The T-cell response to CS and the response to FITC-SC is cross reactive. Lymphocytes or macrophages are usually used to produce these responses and it is thought that a cell surface protein coded for by the H-2 major histocompatibility locus is altered by the hapten and is the antigenic stimulus.

Inbred mice immunized by either subcutaneous injection of 1-3 x 10^7 FITC-SC or contact sensitized with FITC were challenged 6 days later by footpad injection of 1 x 10^7 FITC-kidney cells (FITC-KC). CMI was quantitated by degree of footpad swelling. CS mice had a 24.3 x 10^{-3} inch footpad increase compared to 12.1 x 10^{-3} inch in unimmunized controls ($p<.001$). FITC-SC immunized mice had a 20.2 x 10^{-3} inch increase compared to 13.8 x 10^{-3} inch in controls ($p<.005$). However mice immunized with up to 6 x 10^7 FITC-KC by subcutaneous, intraperitoneal, or iv route and challenged with footpad injection of FITC-KC or FITC-SC did not react.

T-lymphocyte responses can be elicited but not induced against FITC conjugated renal cells in vivo. FITC is thought to modify cell surface proteins shared by lymphocytes and renal cells. T-cell mediated immunity may have a role in drug induced tubulointerstitial nephritis if drugs bind to renal cells and act as a hapten.

ARE URINARY IMMUNE COMPLEXES OF DIAGNOSTIC VALUE? Demetrius Ellis, Irene Stachura, and R.H. Kelly*. Univ. of Pittsburgh School of Medicine and Allegheny General Hospital, Pittsburgh, Pa.

Circulating immune complexes (CIC) may be detected in patients with a variety of diseases and their presence is of limited diagnostic value. The purpose of our study was to evaluate the diagnostic usefulness of urinary immune complexes (UIC) in patients with histologically different forms of glomerular disorders. Corresponding urine and serum samples were available from 52 patients. Urines obtained from 62 patients with non-glomerular diseases served as control for UIC. Agarose gel electrophoresis was used for immune complex (IC) screening. (Clin. Chem. 26:396,1980) The results are shown below:

	No.	CIC	UIC
Control	62	-	0
Minimal change disease	15	0	0
Focal glomerular sclerosis	5	3	0
Mesangial proliferative GN	4	3	0
IgA Nephropathy	6	1	1
Membranous glomerulopathy	7	5	3
Poststreptococcal GN	6	6	2
Membrano-proliferative GN	5	3	2
Rapidly progressive GN	4	3	2
Total	52	24	10

These preliminary results indicate that UIC occur only in patients with glomerular diseases. Passage of IC through filtering structures of the kidneys may reflect focal or diffuse increase in the permeability of glomerular basement membranes. We believe that determination of UIC may be helpful in clinical assessment of patients with glomerular diseases.

● GLOMERULAR PERMEABILITY - SYNTHESIS OF CHARGE BARRIER COMPONENTS BY GLOMERULAR CELLS. Federico M. Farin and Gary E. Striker.* Univ. of Washington, Dept. of Path., Seattle, Washington.

It has been emphasized that charge is a critical determinant of glomerular permeability. Alterations in charge have been noted in human and experimental glomerular diseases associated with proteinuria. Thus the constituents of the charge barrier and their site(s) of synthesis are important issues. Although negative charges have been detected on both epithelial and mesangial cell surfaces and on the glomerular basement membrane, their precise chemical nature is largely unknown. Studies indicate that highly charged glycosaminoglycans (GAGs) such as heparan SO_4 can be isolated from whole glomeruli in vivo, however no information is available on the cellular site of synthesis. To investigate this we isolated human glomerular visceral epithelial and mesangial cells and examined their GAG synthesis in vitro. Confluent cultures were pulse labeled with [^{35}S] SO_4, GAGs were isolated by pronase digestion of the native proteoglycan, identified by cellulose acetate electrophoresis and specific enzymatic and chemical degradation. Both the epithelial and mesangial cells produce GAGs but their biosynthetic profiles are considerably different. The major GAG found in the epithelial cell layer was heparan SO_4 with minor amounts of chondroitin-4 SO_4 and chondroitin-6 SO_4. In the mesangial cell layer, the major GAGs were chondroitin-4 SO_4 and chondroitin-6 SO_4 with only a small amount of heparan SO_4 detected. In view of their biosynthetic profile in vitro, these data suggest that glomerular visceral epithelial cells are a major contributor to the synthesis of heparan SO_4 found in glomeruli.

IN VITRO STUDIES OF CULTURED HUMAN ENDOTHELIAL CELLS IN THE CONTEXT OF GLOMERULONEPHRITIS. H. Fillit*, E.Jaffe*, and J.B.Zabriskie* (intr.by K.Stenzel) Rogosin Kidney Center, New York Hospital Cornell Medical College and The Rockefeller University, New York, N.Y.

Model studies to investigate the cause of endothelial cell injury and proliferation in glomerular disease were performed using human umbilical vein endothelial cells. Microassays for chromium 51 release and terminal tritiated thymidine labelling were used in conjunction with phase contrast microscopy. Immune complexes(either aggregated human IgG or bovine serum albumin and human antiserum) did not cause chromium release; some increase in thymidine labelling was noted. Group A streptococcal cell membranes and purified lipoteichoic acid did not cause chromium release, but did cause a dose dependent reduction in thymidine labelling. Phase contrast microscopy clearly showed cell injury. Purified group A streptococcal carbohydrate did not cause thymidine labelling alterations. Clostridial neuraminidase and glomerular basement membrane induced dose dependent increases in thymidine labelling of subconfluent endothelial cells, associated with enhanced growth by phase microscopy. In summary, some microbial antigens alone induce endothelial injury, while others have no effect, or may induce proliferation. Immune complexes, per se, do not appear to induce endothelial cell injury. We suggest that the in situ glomerular deposition of free antigen may contribute to glomerular pathology by direct effects of antigen on glomerular cells. Studies employing glomerular cells are currently underway in our laboratory.

LYMPHOCYTE CHEMOTAXIS IN RENAL TRANSPLANT AND HEMODIALYSIS PATIENTS. Senih M. Fikrig,* Monica M. Beyer, Yasmin Bhassin, *Kamala Suwtheralingem,* Khalid M.H. Butt, and Eli A. Friedman. State Univ. of N.Y., Downstate Med. Ctr., Depts. of Pediatrics, Medicine and Surgery, Brooklyn, N.Y.

Kidney allografts evoke both cellular and humoral immune responses. T lymphocytes that invade the transplanted organ play a major role in the process of rejection. These cells may be present en passant, or may be attracted by chemotactic factors induced by tissue injury or immune mechanisms. The possibility of a humoral and/or cellular-T lymphocyte chemotactic factor was investigated in stable post renal transplant (SRT) patients, patients undergoing acute (ARAR) or chronic (CRAR) renal allograft rejection, and compared with normal control (C) subjects and patients on hemodialysis (HD). The chemotaxis of T lymphocytes was measured according to the technique described by Parrot et al.

	Lymphocyte Migration, μm/3 hr.			
Grp.	Gey's Sol	Casein	Zy/PHS**	ZY/PS***
C (31)*	14 ± 3	106 ± 10	102 ± 13	93 ± 24
HD (12)	17 ± 3	108 ± 15	98 ± 23	114 ± 11
SRT (11)	11 ± 3	102 ± 8	103 ± 13	98 ± 13
ARAR (10)	13 ± 1	91 ± 17	82 ± 20	84 ± 26
CRAR (1)	15	74	110	82

*Number of subjects **Zymosan/Pooled human serum ***Zymosan/Patient serum

We therefore conclude that chemotactic response of T lymphocytes from transplanted patients in stable condition or undergoing rejection, is no different from the chemotactic response of T cells from normal subjects or patients on hemodialysis. Furthermore, the sera of all subjects are effective in generating chemotaxis.

● CHARGE OF CIRCULATING IMMUNE COMPLEXES AS A FACTOR IN GLOMERULAR BASEMENT MEMBRANE LOCALIZATION. Gloria R. Gallo, Teresa Caulin-Glaser, and Michael E. Lamm. New York University School of Medicine, Dept. of Pathology, New York, N.Y.

The effect of the charge of circulating immune complexes (ICs) on the glomerular localization was investigated in a model of passive serum sickness in BALB/c mice. ICs of electrophoretically heterogeneous or restricted cationic or anionic net charge were prepared in vitro from bovine gamma globulin (BGG) antigen (Ag) and rabbit anti-BGG antibody (Ab) in 5 times excess Ag. Two methods of varying the net charge of ICs were employed: by isoelectric focusing of Ag and Ab, and by chemical modification of the Ag. The relationship between charge and localization was best studied with ICs made with unmodified focused fractions of Ab (pI 2.5-5.0, 6.5-7.0, > 8.0) and the chemically modified cationic or anionic Ag. The distribution of the ICs in the kidney 1 hr after intravenous injection was compared by immunofluorescence and electron microscopy. The cationic but not the anionic or heterogeneous ICs deposited in the glomerular basement membrane (GBM) of peripheral capillaries. The binding of the ICs in subepithelial and subendothelial sites corresponded to the known distribution of structural anionic sites in the GBM. These observations suggest that electrostatic interactions between fixed anionic sites and ICs may be important in the glomerular trapping of ICs.

CIS-PLATINUM (DDP) NEPHROTOXICITY: EFFECT OF CONCURRENT DIETHYLDITHIOCARBAMATE (DDTC) ON GFR, PROXIMAL TUBULAR FUNCTION AND HISTOLOGY. Donald C. Houghton, W. Clayton Elliott, Samuel R. Newcom*, and William M. Bennett. Univ. of Oregon Hlth. Sci. Ctr., Dept. of Med., Portland, Oregon.

DDTC, a compound related to disulfiram, has been reported to reduce the nephrotoxicity of DDP in rats (Proc Nat Acad Sci 76:6611, 1979). To better characterize this phenomenon, we administered 750 mg/Kg DDTC to male SD rats 45 minutes after 7.5 mg/Kg DDP intraperitoneally. At sacrifice five days later, one kidney from each animal was sliced and incubated in Cross and Taggart media for 90 minutes with added para-aminohippurate (PAH) and N-methylnicotinamide (NMN). PAH and NMN uptake were expressed as slice to media ratio (SM).

Rx	N	BUN	Scr	PAH SM	NMN SM
None	6	15±1.9	.68±.09	11.4±1.1	5.0±.5
DDTC	6	13±1.3	.73±.10	12.1±1.9	4.1±.5*
DDP	6	383±97*	7.2±2.1*	3.1±.7*	2.9±.5*
DDP+ DDTC	10	188±95*,†	5.0±2.2*	5.3±2.3*,†	3.4±.6*

*p<.05 compared to untreated controls.
†p<.05 compared to DDP group.
Scr: serum creatinine.

Histologic examination revealed widespread, acute, proximal, tubular necrosis. There was no difference in extent or distribution in the DDP and DDP + DDTC groups.

We conclude that DDTC has only minimal effect on DDP nephrotoxicity at the doses and intervals examined.

EXPERIMENTAL GOODPASTURE'S DISEASE (GPD) IN THE RABBIT. LuJean Jennings*, Giuseppe Andres, and Jan Brentjens*, Dpts. of Path., Microb., and Med., SUNY at Buffalo, Buffalo, New York.

GPD in man is characterized by nephritis and pneumonitis, both mediated by antibodies (Abs) reactive with glomerular (GBM) and alveolar basement membrane (ABM) antigens. Attempts to reproduce this disease in animals have been inconclusive. The aim of this study was to test the hypothesis that increased permeability of the alveolar endothelial cell lining is needed before Abs may bind to ABM. A goat (Gt) antiserum was prepared against rabbit ABM. After i.v. injection of the gamma globulin (GG) fraction into rabbits, GtIgG could be detected by direct immunofluorescence technique (DIF) in GBM, but not in ABM. Absence of binding of ABM Abs to lung was confirmed by paired label isotope technique (PLI). However, 17 of 19 rabbits, injected after exposure to 100% O_2 for 64 hours, were found by DIF to have linear binding of GtIgG along ABM. By PLI, uptake of anti-ABM Abs in lung far exceeded that in kidney. Animals showing extensive localization of GtIgG in lung died with fulminant pulmonary edema and hemorrhagic pneumonitis 15-20 minutes after injection. Light and electron microscopic studies indicated that the lesions in lung of these rabbits were more severe than those found in lung of rabbits exposed to 100% O_2 and injected with the serum GG fraction of a non-immunized goat. None of the latter animals died with pulmonary edema; none were found to have binding of GtIgG in lung. The results indicate that in normal condition the endothelium is a barrier which prevents binding of Abs to ABM. The increased permeability induced by O_2 is a non-immunologic factor which allows the development of GPD.

ALTERED LOCALIZATION OF TUBULOINTERSTITIAL IMMUNE COMPLEXES INDUCED BY INCREASED GLOMERULAR PERMEABILITY. Takeo Ishidate*& John R. Hoyer. Harbor-UCLA Medical Ctr., Dept. of Pediatrics,Torrance,California.

Tubulointerstitial immune complex nephritis with granular deposits of rabbit IgG and Tamm-Horsfall protein(TH) at the base of cells of the thick ascending limb of Henle's loop(ALH) is produced in rats passively immunized with antisera to TH(Kidney Int.14:711,1978). The effect of passage of anti-TH antibodies into the glomerular filtrate on immune complex deposition was studied in rats with two forms of experimental proteinuria. Forty renal specimens from 17 proteinuric rats injected with rabbit anti-TH 10 days after injection of aminonucleoside of puromycin or with sheep anti-proximal tubular FxlA(passive Heymann nephritis) were studied by immunofluorescence from 4 hours to 21 days later. At all times,basal ALH immune deposits were reduced compared to control rats injected only with anti-TH. Proteinuric rats in both models showed marked linear and granular rabbit IgG and TH deposits on the luminal surface of ALH cells. After clearance of antibodies from serum, luminal deposits rapidly decreased during the 2nd and 3rd weeks. These studies provide further evidence for *in situ* formation of tubular immune complexes and demonstrate the critical role of accessibility to anti-TH antibodies in determining the sites of immune complex localization.

A NEW GLOMERULAR ANTIGEN (ag) IN PASSIVE HEYMANN'S NEPHRITIS (PHN). K. Jeraj,* B. Ferrara,* R.L. Vernier, and A.F. Michael, Dept. of Pediatrics, Univ. of Minnesota, Minneapolis, MN.

Although there is evidence for in situ subepithelial immune complex (IC) formation in PHN, the precise location, nature of the ag and pathogenesis of in situ IC formation is unknown. We have defined another antigen-antibody system involving the endothelial region (EnR) of the glomerular capillary (GC). Within 20 min. following an intravenous (IV) injection (inj) of each of four different preparations of 10 mg of rabbit or sheep IgG containing antibody to rat proximal tubular brush border ag (anti-FX1A) to Lewis rats, rabbit IgG was observed along the EnR by immunofluorescence (IF) techniques on 1 μ sections and by immunoelectron microscopy. Following left renal artery perfusion with anti-FX1A similar findings were observed only in the left kidney. Over the course of the subsequent 24 hrs the RIgG was lost from the EnR. After an initial inj of anti-FX1A rats were reinjected on days 2,4,6 & 26. Renal tissue examined 20 min. following the second inj failed to show RIgG along the EnR suggesting loss of these antigenic determinants. These studies demonstrate the presence of ag(s) along the EnR of the GC which reacts with antibody present in anti-FX1A. These antigenic determinants were demonstrated by renal artery perfusion or IV inj of anti-FX1A but not by indirect IF on tissue. The ag(s) was not detectable for periods up to 26 days after a prior inj of anti-FX1A. We speculate that this previously unrecognized antigen-antibody system may be involved in the development of subepithelial IC and/or modification of GC permeability.

● MESANGIAL DISPOSAL OF FERRITIN IN RAT GLOMERULI. M.Kashgarian, D.Biemesderfer*, M.Perfetto*, R.B. Sterzel. Yale Univ. Sch. of Med.-VA Med. Center, Depts. Pathol., Med., & Physiol., New Haven, CT.

The mechanism of glomerular clearing of macromolecules was studied using native horse spleen ferritin (F) as a probe. Thirty Sprague-Dawley rats received i.v. 100mg of F. Renal tissue was examined at intervals from 1 min to 28 days (d) by immunofluorescence (IFM), light (LM), electron microscopy (EM) and histochemistry for ∝-naphthol-butyrate esterase. By IFM, the biodegradable protein component apo-F was first noted in glomeruli at 1 min, was prominent by 6 hrs and became undetectable at 7 to 14 d. By LM, glomerular staining for iron was first seen at 3 to 6 hrs, was strongest by 1 d and did not change through d 28. Apo-F and iron were localized in a mesangial pattern including stalk and lacis area. By EM, F was found in the lamina rara interna from 1 min to 3 hrs. F entered the mesangial matrix within 1 min and mesangial cells by 30 min. The matrix became free of F at 1 to 3 d. Intracellular F appeared initially as native F in phagolysosomes and later only as condensed iron cores. No shift of F from the tuft to vascular pole was observed. The macula densa cells remained free of F. Few monocytes with F in many lysosomes were seen in the capillary lumen. The highest mean glomerular count of esterase-positive monocytes was 1.3 per tuft on d 3 (controls 0.2) at a time when most cells in the mesangium showed F uptake by EM. The results demonstrate that (1) the glomerulus disposes of F by degradation of apo-F by mesangial cells and lysosomal storage of iron; (2) there is no appreciable removal of F from the glomerulus via the vascular pole; (3) the contribution of infiltrating monocytes to the disposal of immunologically inert F appears small.

● HIGH FAT DIET ACCELERATES LUPUS NEPHRITIS IN AUTOIMMUNE MICE. Vicki E. Kelley and Shozo Izui*. Univ. of Pittsburgh Sch. Med., Pgh, PA and Scripps Clinic and Research Foundation, LaJolla, CA.

Dietary factors are reported to influence the development of renal disease in autoimmune mice. These studies were designed to evaluate the effect of high fat diet (HF) on immune complex mediated lupus nephritis. NZB/W mice (n>60) were fed a HF diet rich in saturated (S) (25% lard, 5% cholesterol) and unsaturated fat (20% corn oil) and compared with similar numbers of animals on a control diet (4.5% fat). Results are presented in this table:

		7 month values			
Diets	Mortality (50%)	sc (mg/dl)	↑Urinary Protein(%)	↑BUN (%)	Lipids in glomeruli(%)
HF-S	9 mo.	265	71	25	79
Control	11 mo.	133	16	0	19

Mice on HF diets died sooner than controls. The increase in dietary fat elevated serum cholesterol (sc) levels and accelerated the loss of renal function. Morphologic evaluation by light and fluorescence microscopy showed that deaths were caused by immune complex glomerulonephritis. Ultrastructural examination of glomeruli from mice on HF diet revealed lipid in the glomerular basement membrane of peripheral loops and in the mesangium in areas with immune complexes. This increased lipid deposition was confirmed by histochemical staining of glomeruli and by biochemical extraction. Accelerated renal disease was not associated with changes in circulating ss or ds DNA antibodies, immunoglobulins, total immune complexes or immune complexes to retroviral gp70. In conclusion, HF diets promote immune complex lupus nephritis in NZB/W mice. These studies suggest renal disease in accelerated by the accumulation of lipid in glomeruli containing immune complexes.

● REDUCTION IN ENDOTHELIAL FENESTRAE (EF) NUMBER AND SURFACE AREA DOES NOT IMPEDE LUMEN-MESANGIAL TRANSFER OF IMMUNE COMPLEXES (IC). W.F. Keane and L.Raij, Dept. of Med., Univ. of Minnesota, Mpls, MN.

If, as postulated, IC gain access to the mesangium (MES) primarily through EF, a reduction in EF number and/or surface area should decrease capillary lumen-MES traffic of IC. In rats, both gentamycin (G; 40 mg/Kg b.w. i.p. x10 days) and uranyl nitrate (UN; 25 mg/Kg b.w. i.v. x1 dose) induce a >50% reduction in the number and surface area of EF (JCI 65:1980) and a reduction in the ultrafiltration coefficient with a decrease in GFR, in spite of a preserved RBF. Thus, we studied MES uptake and disappearance of radiolabelled aggregated human IgG (AG) (biologically akin to immune complexes) in control (C), G and UN rats.

Twenty C, 20 G, and 20 UN rats were given 45 mg/100 Gm b.w. of AG i.v. and sacrificed at 2,4,8 and 24 h after injection. MES AG was measured in preparations of pooled, isolated glomeruli and compared to simultaneous blood levels of AG>7S.

Results:	MES AG (μg/mg)		
Time	Control	G	UN
2 h	10.1	8.8	9.4
4 h	8.5	9.3	8.8
8 h	5.2	5.6	5.4
24 h	0.4	0.5	0.5

Blood levels of AG>7S were similar in C,G and UN rats. Inulin clearance was 1.05, 0.63 and 0.34 and RBF (flow probe) was 5.48, 4.68, 5.32 ml/min Gm k.w. in C,G and UN, respectively. These studies demonstrate that the lumen-MES transfer of AG is unimpeded in spite of a major reduction in EF number and surface area. This suggests that IC may travel primarily through the MES-endothelial interface, an area that could have different permeability characteristics than the rest of the capillary.

INFLUENCE OF AGE ON THE DEVELOPMENT OF TOLERANCE TO HEYMANN NEPHRITIS. Kanwal Kher,* S.P. Makker, I.J. Kirson*. Case Western University, Cleveland, Ohio.

Newborn Lewis rats (NL) were given FxIA 3 mg/10 gm rat wt. dissolved in 0.2 ml saline and emulsified with 0.2 ml incomplete Fruend's adjuvant (IFA). Three intraperitonial injections (IP) consisting of 0.15 ml, 0.15 ml and 0.1 ml emulsion were given on the 2nd, 3rd and 4th days, respectively. Five adult Lewis rats (AL) were also pretreated in the same manner using 30 mg FxIA per 100 gm rat wt. As a control, one group of rats was not pretreated neonatally. All groups were challenged with 10 mg FxIA and complete Freund's adjuvant (CFA) 6 weeks after pretreatment, and a second challenge was given 4 weeks later. Urinary protein was estimated biweekly. A renal biopsy was taken 12 weeks after the first challenge of FxIA and CFA and was evaluated for glomerular immune deposits of IgG (GID) by immunofluorescence using a semiquantitative score of 0-4+.

	Control	NL pre-RX	AL pre-Rx
Proteinuria	11/13	4/13	0/5
GID 3+	11/13	3/13	0/5

Both the NL and AL pre-Rx groups showed a significant reduction in the number of animals that developed proteinuria. All but one rat in NL pre-Rx and all in AL pre-Rx groups demonstrated GID, but the intensity of fluorescence and the amount and density of the GID was suggestive of only a mild disease (Trace-2+). These observations demonstrate that pretreatment with FxIA and IFA can significantly reduce the incidence of Heymann nephritis and that newborn Lewis rats are immunologically competent to stimulate the mechanism(s) responsible for the development of this tolerance.

SPECIFIC ROLE OF INCOMPLETE FREUND'S ADJUVANT IN INDUCING TOLERANCE TO HEYMANN NEPHRITIS IN NEONATAL RATS: Kanwal Kher,* S.P. Makker, I.J. Kirson.* Case Western Reserve University, Cleveland, Ohio.

Newborn Lewis rats were injected with a saline suspension of 3 mg FxIA per 10 gm of rat wt. intraperitoneally (IP) for 3 days. Another group (NP) received IP injections of FxIA emulsified with incomplete Freund's adjuvant (IFA). A 3rd group received no pretreatment (C), and a 4th group received only IFA. At 6 and 10 wks all groups received 2 injections of 10 mg FxIA with complete Freund's adjuvant (CFA). 24 hr urinary protein was assessed biweekly. A renal biopsy taken 12 wks after the first challenge with RTA and CFA was assessed for immune deposits (GID).

	C	NP	FxIA only	IFA only
Total Number	13	13	7	11
Proteinuria	11	4	6	7
p Value for proteinuria		0.01*	0.05**	***
3+ or GID	11	3	6	6

*Significance derived between 'C' and 'NP' groups
**Significance derived between 'NP' and FxIA groups
***Statistically non-significant when compared with 'C'

Proteinuria was significantly lower in 'NP' while 'FxIA' group showed no significant alteration from the control. Although glomerular immune deposits were present in NP group, the extent of distribution and amount of these deposits were considerably less compared to the 'C' and 'FxIA' groups. This work suggests that 'FxIA' alone is unable to induce tolerance to the disease in Heymann nephritis and that IFA plays a specific role when combined with FxIA.

THE PREVENTION OF HEYMANN NEPHRITIS (AICN) USING CYCLOSPORIN A (CsA). I.J. Kirson*, S.P. Makker, K.K. Kher*. Case Western Reserve University, Cleveland, Ohio. (Intro. by R.D. Adelman)

CsA (a novel immunosuppressive) was given to 4 groups of Lewis rats (100 mg/kg/day), each for 4 consecutive days at various times in relation to immunization with renal cortical fraction (Fx1a) + Complete Freund's Adjuvant. All groups were immunized on day 1 and 28. Groups I and II received CsA 24 hours before, and 48 hours after the 1st immunization, respectively. Group III received CsA 7 days after (once brush border antibody was present), and Group IV 6 weeks after 1st immunization, respectively. A control group immunized similarly received no CsA.

Abnormal proteinuria and glomerular immune complex deposition constituted criteria for disease. 2/17 experimental and 20/20 control rats developed abnormal proteinuria. Renal biopsies done 14 weeks after the 1st immunization showed IgG deposits in 2/4 Group I, 1/5 Group II, 3/3 Group III, and 2/5 Group IV. 20/20 control rats had IgG deposits. C_3 deposits were present in 17/20 controls and 0/9 Groups I and II, and 5/8 Groups III and IV. To rule out generalized immunosuppression, hemagglutination titers to sheep RBC's was obtained in all animals 10 weeks following the 1st immunization (4-9 weeks after CsA administration). The hemagglutination titers between control and experimental groups were comparable, suggesting lack of generalized immunosuppression at that time.

CsA is therefore capable of altering the course of Heymann nephritis by specific immunosuppression, depending in part on when given in relation to antigen exposure. The effect of the drug, however, seemed to persist long after being discontinued.

● FOCAL SEGMENTAL GLOMERULOSCLEROSIS IN PATIENTS WITH UNILATERAL RENAL AGENESIS. Dobri D. Kiprov,* Robert B. Colvin,* and Robert T. McCluskey, Dept. of Pathology, Massachusetts General Hospital, Boston, MA

The clinical course and pathologic findings of seven patients with unilateral renal agenesis who developed focal segmental glomerulosclerosis (FSG) in their solitary kidneys are described. A review of 586 surgical pathology renal specimens (452 biopsies and 134 nephrectomies) revealed 28 (4.7%) cases of FSG, four of whom had unilateral renal agenesis ($p < 0.0001$). The glomerular lesions were characterized by focal and segmental scarring and adhesions in glomeruli, IgM and C3 deposition by immunofluorescence, and foot process loss and capillary collapse by electron microscopy. Two of the patients with unilateral renal agenesis and FSG were father and son. None of the patients had clinical or morphological signs of reflux nephropathy. A review of 6000 autopsies revealed seven examples of unilateral renal agenesis; two (29%) died of chronic renal failure due to FSG and five did not have FSG. In contrast, nine patients who died 8 to 46 years after adult unilateral nephrectomy had no glomerular disease. Our study suggests that patients with unilateral renal agenesis are more likely to develop FSG than patients with two kidneys. These findings are in accord with studies in animals in which early nephrectomy promotes FSG. The glomerular damage may result from some phenomenon related to "glomerular overload" or from an unknown factor, possibly genetic, which caused both the unilateral renal agenesis and the FSG. Unilateral nephrectomy did not promote FSG.

● A DISTINCTIVE LESION OF THE CORTICAL COLLECTING TUBULES (CCT) WITH CHRONIC LITHIUM (Li) TREATMENT IN RATS. Mitchel A. Kling*, J.G. Fox*, S.M. Johnston*, N.T. Rubin, R.H. Rubin*, and R.B. Colvin*: Mass. Gen. Hosp., Depts. Path. and Med., Boston, MA and Mass. Inst. of Tech., Dept. Nutr. and Food Sci., Cambridge, MA.

Some patients on Li therapy have developed chronic interstitial nephritis; similar lesions were reported in Li-treated rats. The present study further characterizes the putative Li nephropathy. Male Wistar rats were given a casein diet with 90 mEq/kg dry wt. of Li_2CO_3 or Na_2CO_3 (pair-fed controls) and had free access to water and 2.7% saline. Animal weights, food and fluid intake were monitored and urine collected at intervals from 0-18 weeks. Serum Li levels were stable at $0.95 \pm .06$mEq/l. Li-treated rats developed polydipsia and increased saline intake by 3 weeks; free water clearance was markedly increased (80 ± 12 ml/24h vs -60 ± 3 in the controls). Focal dilation of the CCT was seen in the Li-treated rats. The tubular cells showed a number of changes, including nuclear enlargement and pleomorphism, mitotic figures, binucleate cells, apical cytoplasmic basophilia, irregular bulging and flattening. Changes were first observed at 3 weeks but were more pronounced at 9 and 18 weeks, with the appearance of intratubular mononuclear cells, basal vacuolization, and occasional necrosis of tubular cells. No abnormalities were detected in the interstitium, vessels, glomeruli, or other tubules. The injury to the CCT, which appeared to be partially compensated by increased tubular cell proliferation, may render the kidney more susceptible to otherwise mild insults, and may explain the infrequent occurence of renal failure in Li-treated patients.

● PREVENTION OF DIABETIC NEPHROPATHY BY DIET CONTROL IN THE db/db MOUSE. Stanley M. Lee* and R. Bressler*, Univ. of Arizona, Dept. of Med., Tucson, Arizona. (intr. by M. Katz)

Diabetes in the C57 BLKsJ db/db mouse is initially expressed as hyperinsulinemia, which is followed by hyperphagia, progressive obesity and pathologic abnormalities in several organ systems. This study was designed to evaluate the effects of metabolic control on the natural history of the diabetic nephropathy. Beginning at one month of age, and continuing for twelve weeks, diabetic mice were subjected to controlled dietary restriction, such that their weight was maintained similar to that of age matched non-diabetic heterozygotes. Diet restricted diabetics (D) were compared with diabetics fed ad lib (C) and heterozygote non-diabetics (H).

Group C evidenced well defined renal lesions, which included 3+ to 4+ immunoglobulin deposition in the glomerular mesangium, and generalized mesangial matrix expansion. These lesions were completely prevented in Group D, whose glomeruli were normal by light microscopy, and demonstrated trace to 1+ mesangial immunoglobulin deposition,-features identical in all respects to the non-diabetics (H).

Significant lowering of glycosylated hemoglobin, fasting blood glucose and water intake was achieved by diet restriction, and plasma insulin was dereased, but not normalized. Enhanced efficiency of food utilization was demonstrated by Group D, who consumed approximately half that of Group H, while maintaining a similar weight. These results indicate that diabetic control achieved by prevention of obesity in the db/db mouse successfully precludes the development of nephropathy.

● INFLUENCE OF ANTIBODY (Ab) CHARGE AND CONCENTRATION ON SUBEPITHELIAL IMMUNE DEPOSIT (SID) FORMATION. M.P. Madaio,* D.J. Salant, W.G. Couser, C. Darby,* and N. Capparell.* Boston Univ. Med. Ctr. Boston,MA

In experimental membranous nephropathy produced in rats by heterologous Ab to tubular brush border antigen we have shown that SIDs can represent Ab binding to a fixed glomerular antigen.In addition, the inverse relationship of glomerular Ab binding (GAb) to Ab size established a role for the size-selective glomerular filtration barrier in this process. The role of Ab charge in SID formation was studied using IgG Ab eluted from autologous immune complex nephropathy rat kidneys and separated by ion exchange chromatography into cationic (PK+,pI 6.1-8.9) and anionic (PK-, pI 4.2-6.2) fractions. Equal amounts of ^{125}I PK+ and ^{131}I PK- were administered in varying doses to 10 rats. At 24 hrs GAb of each PK was directly related to blood concentration of IgG (r=.86 and .90). GAb of PK+ was 2.2-5.0 times greater than PK- over the range of Ab concentrations studied ($p<.001$); the differences being 3 fold at the mean blood level. Preferential glomerular binding of cationic antibody was sustained over 5 days in a separate sequential study. These results could not be explained by a difference in Ab content of the 2 fractions;repeated incubations with normal rat glomeruli resulted in absorption of 83.7±5.5% of PK+ and 83.3±5.3% of PK-(vs 37.3±2.6% of acid-treated normal IgG)demonstrating specific *in vitro* binding and equal Ab content of the eluate fractions.

We conclude that the amount of *in situ* SID formation in experimental membranous nephropathy is influenced by both the concentration and charge of pathogenic Ab,and that charge as well as size-selective properties of the glomerular filter influence the formation of subepithelial deposits.

TOTAL LYMPHOID IRRADIATION(TLI)INDUCES SUPPRESSORS OF T CELL RESPONSIVENESS BUT FAILS TO ALTER THE COURSE OF EXPERIMENTAL NEPHRITIS. R.P.Lowry,* K.E.Gurley,* C.B.Carpenter, J.A.Belli*& J.P.Merrill. Peter Bent Brigham Hosp.Boston,MA(Intr.by J.Seely)

TLI has recently been shown to facilitate the development of specific suppression, and to retard the progression of spontaneous nephritis in NZB/NZW mice. Accordingly we studied the effects of TLI on the immune system of LEW rats, and on the course of Nephrotoxic Serum(NTN)and Autologous Immune Complex (AICN) Nephritis,analogous to human anti-GBM and Membranous disease, respectively. TLI (200 rad/day, 3400 rads total dose) was administered using a shield supplied by Dr.S.Strober. TLI induced leukopenia, with relative lymphopenia and monocytosis (TLI 38±3% monocytes vs 14±3% controls). Response to mitogen (PHA) and in mixed lymphocyte culture, markedly depressed early post TLI (Δ cmp < 10% N), normalized over 6 weeks. Mixing experiments demonstrated the presence of suppressor cells early post TLI,capable of suppressing in vitro T cell responses, and these were characterized as being glass wool adherent and radiation resistant (3000 rads). The effect of TLI on established NTN and AICN was assessed by urinary albumin, serum creatinine and survival. TLI exerted no significant beneficial effect on the course of NTN, survival correlating only with the serum Cr. at the onset of irradiation ($p<.005$). Accelerated mortality was noted in rats with AICN treated with TLI. Light and Immunofluorescent examination of kidneys of NTN and AICN rats treated with TLI was virtually identical to that of untreated controls. In spite of a profound degree of in vitro unresponsiveness, apparently mediated by an adherent mononuclear cell, TLI failed to ameliorate the course of experimental nephritis.

● COMPARATIVE STUDY OF SUBEPITHELIAL IMMUNE DEPOSIT (SID) FORMATION IN ACTIVE (AICN) AND PASSIVE (PHN) HEYMANN NEPHRITIS. M.P. Madaio*, D.J. Salant, M.M. Stilmant, C. Darby*, N. Capparell* and W.G. Couser. Boston Univ. Med. Ctr., Boston, MA.

Active and passive immunization of rats to tubular brush border antigen (Fx1A) produce SIDs indistinguishable from membranous nephropathy. Studies in the PHN model have shown SID formation can occur *in situ* due to anti-Fx1A IgG binding to a fixed glomerular antigen. In AICN the role of this mechanism vs. circulating immune complex deposition remains controversial. We studied this question by comparing the properties of heterologous (sheep) anti-Fx1A IgG (HAb) with rat IgG eluted from AICN kidneys (AAb). HAb and AAb bound to proximal tubular brush border and to capillary walls of isolated glomeruli in cryostat sections by IF. ^{125}I HAb and AAb bound specifically to isolated glomeruli (HAb 2.5X, AAb > 8X more than control IgG). After i.v. administration of ^{125}I labelled HAb or AAb, the disappearance from blood and glomerular uptake of Ab were similar, and they both produced SIDs by IF. HAb bound to glomeruli *in vivo* was able to competitively inhibit the binding of AAb; when glomeruli containing increasing amounts of *in vivo* deposited ^{125}I HAb were isolated and incubated with a fixed quantity of ^{131}I AAb, there was an inverse relationship of AAb to HAb bound ($r= -.573$, $p<.01$).

We conclude that eluted AAb reacts very similarly to HAb *in vitro* and *in vivo*. Both Ab's produce SIDs *in vivo* and apparently bind to the same antigenic sites in the capillary wall. The results suggest that the SIDs in AICN can be formed by the same *in situ* mechanism previously demonstrated in PHN.

LACK OF DEMONSTRATION OF BRUSH BORDER ANTIGEN (BBAg) OF HEYMANN NEPHRITIS (HN) IN CULTURED RAT GLOMERULI. S.P. Makker, I.J. Kirson,* A.Petrulis,* A. Bruzel* and K. Kher.* Dept. of Pedia. & Med., Case Western Reserve Univ. Sch. of Med., Cleveland, Ohio.

Conflicting data exist regarding the presence of BBAg of HN on the epithelial side of the glomerular basement membrane (GBM). A new approach utilizing glomerular cultures was used to study the presence of BBAg in glomeruli. Glomeruli from 4-5 wk. old normal Lewis rats were cultured according to the method of Kreisberg et al. (Kid. Int. 14:21, 1978). Nine day old whole glomerular cultures with outgrowths of epithelial cells were studied by direct immunofluorescence using fluorescein labelled rat brush border antibody (BBAb) and by indirect immunofluorescence using unlabelled rat BBAb. Glomerular cultures were also used as an immunogen and six Lewis rats were immunized in footpads with glomeruli (300,000)/rat) mixed with Complete Freund's adjuvant. Sera were examined wkly. for BBAb response for 4 wks. Appropriate controls including staining of cultured normal proximal tubules and glomeruli from HN rats were used. These techniques easily demonstrated 1) BBAg in the cultured proximal tubules (present as contaminants) and, 2) fine granular fluorescence for rat IgG along the GBM of cultured HN glomeruli validating the appropriateness and usefulness of the techniques for this study. However, BBAg could not be demonstrated in cultured normal glomeruli or in HN glomeruli. Also, no BBAb response was elicited in any of the animals immunized with glomeruli. These data interpreted within the limits of sensitivity of the techniques utilized and the in vitro nature of some of the experiments, fail to show the presence of BBAg in normal glomeruli.

● ALTERATION OF IMMUNE COMPLEX GLOMERULONEPHRITIS BY PROSTAGLANDIN E. Kenneth R. McLeish, Amira F. Gohara*. Medical College of Ohio, Toledo, Ohio.

We have previously reported that prostaglandin ($PG)E_1$ prevents immune complex glomerulonephritis (GN) in mice, but the mechanism of action could not be determined. In the present study we examined the effect of PGE_1 and PGE_2 on the antibody response and the development of GN in Swiss mice receiving daily injections of a foreign protein, apoferritin (APO). The ability of PGE_1 200 µg twice daily or PGE_2 200 µg twice daily to alter GN was assessed by light (LM) and immunofluorescence (IM) microscopy. By LM 9/9 mice receiving APO alone developed proliferative GN. Treatment with PG significantly altered GN with 4/8 mice treated with PGE_1 and 6/10 mice treated with PGE_2 having normal histology. IM revealed extensive, peripheral granular deposition of IgG and IgM in mice receiving APO alone. Treatment with either PGE_1 or PGE_2 resulted in decreased glomerular deposition of IgG while IgM deposition was unchanged. Synthesis of anti-APO IgG was measured by indirect hemagglutination of sera obtained at sacrifice, 4 days after the last injection of APO. Although antibody was present in all mice receiving APO, the titer was significantly lower ($p<0.05$) in mice treated with PGE_1 or PGE_2. We conclude that PGE_1 and PGE_2 significantly alter the development of immune complex GN. Treatment with these PGs decreased IgG deposition within glomeruli and significantly decreased anti-APO IgG production indicating the mechanism of action may involve partial inhibition of the humoral immune response. The mechanism by which PGE inhibit specific antibody production remains to be defined.

● ANTIBODY TO TAMM-HORSFALL PROTEIN IN PORCINE REFLUX NEPHROPATHY. A.R. Mayrer,* L. Dziukas,* C.J. Hodson,* V.T. Andriole. Yale University School of Medicine, New Haven, CT.

Vesicoureteral reflux (VUR) is frequently an asymptomatic cause of progressive renal damage, reflux nephropathy, and chronic renal failure. We studied the kinetics of serum IgG antibody (Ab) to Tamm-Horsfall protein (THP), and correlated this with pyelographic changes and renal function in an established porcine model of reflux nephropathy.

Partially obstructing 3 or 4mm rings were placed around the distal urethra of 19 miniature sows. Intravenous pyelograms (IVP), serum THP-Ab titers by radioimmunoassay, serum creatinines, and bacterial cultures of bladder urine were done at 1 to 2 week intervals for up to 20 weeks.

The results of the time course of the development of abnormal THP-ab titers (>1:16), pyelographic changes, bacteriuria, and abnormal renal function were as follows:

IVP Status	No.	Duration	No. with Titer >1:16	
Normal	10	15±2 Days	0	(0%)
Bladder Dilatation	6	20±6	0	(0%)
Ureteral Dilatation	15	32±5	11	(73%)
+creatinine>1.5mg%	10	50±8	7	(70%)
+bacteriuria	6	54±13	4	(67%)
Renal Scarring	7	71±9	1	(14%)

In summary, elevated serum Ab to THP occurs with the onset of ureteral dilatation; and is a sensitive and specific indicator of VUR in a porcine model. Elevated Ab titers were not affected by concurrent renal insufficiency or bacteriuria. Furthermore, abnormal titers disappeared with the onset of renal scarring. Abnormal Ab to THP may be helpful in detecting the onset of VUR in humans.

ROLE FOR SYNERGISM IN IMMUNE MEDIATED GLOMERULAR INJURY. A. Vishnu Moorthy, Renal Section, V.A. Hospital & Dept. of Medicine & Pathology, Univ. of Wisconsin, Madison, Wisconsin.

The potentiation of immune mediated glomerular injury in Lewis rats receiving 2 different insults namely nephrotoxic α-GBM antiserum (raised in rabbits against rat GBM) and renal tubular brush border antigen (FxlA) (from saline perfused rat kidneys) was studied.

Four groups of Lewis rats were used. Gr I - 6 mg FxlA in complete Freund's adjuvant (CFA) S/C. Gr II - 0.1 ml (1/10th of the toxic dose) of nephrotoxic serum 1/v. Gr III - FxlA (6 mg) in CFA S/C + 0.1 ml nephrotoxic serum 1/v. Gr IV - (1 ml) CFA only S/C + 0.1 ml nephrotoxic serum 1/v. 24 hour urine albumin excretion was measured weekly for 6 wks by radial immunodiffusion using anti-rat albumin anti-serum. The rats were sacrificed at various times and kidney studied with light, immunofluorescence and electron microscopy.

Albuminuria (mg/day ± S.D.)

Gr	1st Wk	3rd Wk	4th Wk	5th Wk
I	.2± .2	.7± .2	.5± .2	.3± .4
II	1.1± .7	2.0± .5	1.9± .7	1.4± .4
III	90.9±61.1	72.3±44.3	57.3±66.9	55.6±66.9
IV	18.5±21.8	73.6±30.4	53.0±19.6	31.5±17.3

Early and persistent albuminuria was seen only in Gr III & IV. Renal pathologic alterations were also more in these rats.

Subtoxic doses of nephrotoxic serum potentiates glomerular injury to FxlA, with early and marked albuminuria. In the presence of subtoxic doses of nephrotoxic serum, rats are susceptible to glomerular injury and exhibit albuminuria when challenged with non-specific immune stimuli such as CFA.

● SUPPRESSION OF INTERSTITIAL NEPHRITIS BY AUTOLOGOUS ANTI-IDIOTYPIC IMMUNITY. E.G. Neilson and S.M. Phillips, Renal and Allergy-Immunology Sect., Dept. of Med., Univ. of Pa., Phila., PA.

Autoimmune responses can be directed against T cell idiotypes associated with antigen-binding receptors. As anti-receptor responses can effectively regulate many antigen-stimulated immune responses, we studied their role in a model of interstitial nephritis. We isolated tubular antigen-reactive lymphoblasts from BN rats to be used as an autoimmunogen to induce anti-idiotypic immunity. Rats were injected five times with either soluble tubular antigen-stimulated T lymphoblasts harvested from other nephritic(N-SRTA) or control(C-SRTA) animals. Both groups were then immunized with renal tubular antigens in adjuvant. 21 days later their kidneys were examined, lymphocytes stimulated with a panel of soluble antigens, and sera tested for anti-idiotypic antibodies utilizing hybridoma derived anti-tubular basement membrane antibodies (MαTBMA) in a SRBC-hemagglutination assay. N-SRTA animals did not develop significant interstitial nephritis by histologic(N-SRTA: 6% cortical involvement vs. C-SRTA: 46%; $p<0.002$) or fluorescent criteria. Lymphocytes from N-SRTA animals also failed to respond to SRTA(N-SRTA: stimulation index=1.5 vs. C-SRTA: 2.9; $p<0.007$) and their sera contained significant titers of antibodies against MαTBMA(N-SRTA: 1:32 vs. C-SRTA: 1:4). Additional controls revealed no significant anti-rabbit response. In summary, these data directly demonstrate that auto-anti-idiotypic immunity against tubular antigen receptors significantly suppresses interstitial nephritis. In addition, involved T cells and antibodies share a common idiotype.

● DAMAGE TO RENAL PROXIMAL TUBULES IN RATS WITH HEYMANN NEPHRITIS FOLLOWING REIMMUNIZATION WITH FxlA. Bernice Noble*, Jan Brentjens, Giuseppe Andres and Judith Van Liew. Depts. of Microbiology, Pathology, Physiology and Medicine, SUNY at Buffalo, New York.

Damage of proximal tubules (PT), apparently mediated by antibodies to brush border (BB), occurs in Heymann nephritis (HN) (Mendrick, et al., Kid. Int. 16:799, 1979). Partial recovery of PT is observed when antibodies to BB disappear from the circulation. The present study evaluated the effect of reimmunization with FxlA during this 'recovery phase' of HN. A booster immunization of 10 mg FxlA given 32 weeks after the initial immunization was followed by a rapid rise in titer of circulating BB antibodies. At sacrifice, 4 weeks after the booster immunization, increased urinary protein excretion and decreased tubular reabsorption of urea, glucose, phosphate and sodium were observed. A rise in serum creatinine concentration was also detected. By direct immunofluorescence (IF) tests, a reappearance of IgG deposition was seen along BB and the basement membrane of PT. Indirect IF tests suggested that substantial loss of BB from PT had occurred. BB antigen was detected in granular deposits along the tubular basement membrane following acid elution of immunoglobulin. Examination of kidneys by light and electron microscopy revealed that severe damage to PT had been sustained. Peritubular fibrosis and distal tubule dilation were also observed. It is concluded that tolerance to BB antigens does not develop in rats with HN. Reimmunization with FxlA rapidly produces severe alteration of PT morphology associated with deterioration of glomerular and tubular function. These findings support the view that damage to PT in HN is mediated by antibodies to BB.

● AGGRAVATION OF EXPERIMENTAL GLOMERULONEPHRITIS BY SUPERIMPOSED CLIP HYPERTENSION. J. Neugarten,* H. Feiner, R.G. Schacht, G.R. Gallo and D.S. Baldwin, N.Y.U. Sch. of Med., Depts. of Med., Path., and Ped., N.Y.

To examine the possible enhancing effects of hypertension on the clinical and morphologic features of glomerulonephritis, two kidney clip hypertension (CH) was superimposed on nephrotoxic serum nephritis (NSN) in Sprague-Dawley rats. The following parameters were assessed: blood pressure (BP), cardiac index (CI=heart weight/100 mgm rat), proteinuria (UpV) and renal morphology. Three to 8 rats from each Group (see Table) were randomly selected and sacrificed at monthly intervals over a 6 month period. The mean values for all sacrifices in each Group were as follows:

Group	n	BP mm Hg	CI	UpV mg/24 hr
1 Control	23	102±1	0.28±0.01	2.7±1.0
2 CH	34	146±2	0.35±0.01	7.8±2.9
3 NSN	20	107±1	0.25±0.01	17.5±5.5
4 NSN+CH	31	143±2	0.36±0.01	107.8±14.8

BP and CI were significantly greater in CH and in NSN+CH than in Controls or NSN ($p<.001$). While only minimal UpV occurred in NSN, the superimposition of CH on NSN resulted in much heavier UpV ($p<.001$). UpV increased during successive months in NSN+CH, while it diminished in NSN. Renal histology in NSN showed mild mesangial proliferation; in CH a few sclerotic glomeruli; however, severe proliferation and sclerosis were observed in NSN+CH.

These results demonstrating the adverse role of CH on NSN may be relevant to the effect of hypertension on the course of glomerular diseases in man.

● IMPORTANCE OF GENETICS IN THE DEVELOPMENT OF AUTOIMMUNE GLOMERULOTUBULAR NEPHROPATHY (AGTN) IN MICE. J.P. O'Reilly*and W.K. Bolton, (intr. by P.I. Lobo) Univ. of Va. School of Med., Charlottesville, Va.

Genetic influences appear to be involved in the development of nephritis in man. We have produced AGTN in Swiss Webster mice and shown that T-cells are required for induction of the lesion. We have extended these studies to further investigate the role of genetics in this model. Twelve strains of mice were selected based on H-2 locus, humoral and cellular immune responsiveness, hormonal status, and reticuloendothelial system function. We immunized 12 each of these strains with human GBM as previously described. Controls received complete Freund's adjuvant. Renal lesions were scored by immunofluorescence (IF) on a 10 part scale for glomerular (G) and tubular (T) basement membrane (BM) linear deposits and mesangial deposits of mouse C-3 fibrinogen, IgG, subgroups γ_1, γ_{2A}, γ_{2B}, γ_3 and IgM. ANF and anti-GBM antibody in serum was tested by IF. Significant differences were present between strains in the amounts of IgG subgroup deposited; pattern of immune response to GBM and TBM between and within strains; in serum GBM antibodies; in development of ANF; in amount of mesangial IgM; and in the distribution of types of IgG sub-groups (all of the above, $p<.05$).

These studies show that genetic constitution is important in the development of AGTN in this model. Further, the H-2 genetically controlled region for immune response in the mouse appears to be involved. By implication, genetically determined immune responsivity may explain differences in the development of nephritis observed clinically in man.

SUBSTITUTION OF RAJI CELLS (RC) WITH SEPHAROSE 4B COATED WITH ANTI-HUMAN C3 ANTIBODY (S4B-AC3) IN THE ASSAY OF CIRCULATING IMMUNE COMPLEXES (CIC).
Masashi Sato* and Takeshi Ozawa, Indiana University School of Medicine, Indianapolis, Indiana

RC are known to bind IC with C3B rectors and proved to be a sensitive tool for quantitating CIC. However, the maintenance of RC is cumbersome in the clinical laboratory. We prepared and examined S4B-AC3 for the RC substitute. CNBr-activated S4B was coupled with rabbit IgG-AC3. The specificity and functions of this preparation were studied by immunofluorescent technic (IFT) and uptakes of human aggregated IgG (HAG) fractionated HAG and bovine serum albumin (BSA) - anti-BSA complexes. Serum samples were obtained from 20 normal volunteers (NV) and 30 systemic lupus erythematosus (SLE), 20 rheumatoid arthritis (RA)and 13 subacute bacterial endocarditis patients (SBE). CIC were quantitated in duplicate as follows: 25 µl of serum sample was diluted with 175 µl of veronal buffer (VB) containing 1% BSA, mixed with 250 µl of 6% polyethyleneglycol (PEG) and centrifuged. After washing, the preciptant was dissolved in 4 ml of 1% BSA.VB and incubated with 0.5 ml of 10% of S4B-AC3 was further incubated with 15 µg of ^{125}I - Goat IgG anti-human IgG and counted. CIC value in NV was 2.0 ± 1.7 mg/ml (Mean ± SD). When the positivity of CIC is defined above 2SD, 19/30 in SE, 19/20 in RA, 12/13 in SBE and 1/20 in NV were positive. IgA and IgM was observed on S4B-AC3 in 2/30 and 4/30 of SLE, 3/20 and 7/20 of RA, 1/13 and 2/13 of SBE and 1/20 and 0/20 of NV, respectively. These results suggest that S4B-AC3 serves as a good tool for quantitation of CIC for its simple preparation, high sensitivity and stability.

ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC): A NEW EFFECTOR MECHANISM IN INTERSTITIAL NEPHRITIS.
S.M. Phillips and E.G. Neilson, Renal-Electrolyte and Allergy-Immunology Sect., Dept. of Medicine, Univ. of Pa., Phila., Pa.

Anti-tubular basement membrane antibodies (αTBMA) passively transferred into normal guinea pigs produces interstitial nephritis. The complete expression of disease, however, also depends on functioning bone marrow cells. We describe here a new pathogenic mechanism for these observations whereby αTBMA provide information to a pre-existing or natural cell-mediated surveillance system thought also to be of bone marrow origin. Chromium labelled, tubular antigen-coated chicken red blood cells were used as targets in an ADCC assay in the presence of αTBMA and normal spleen cells. αTBMA in the sera of nephritic guinea pigs induced more chromium release via ADCC than did sera from controls (23% lysis vs. 9%; $p<0.001$). The αTBMA binding was also specific for species-independent tubular antigens.

The spleen cells involved in this ADCC demonstrated a characteristic dose responsivness and were non-adherent to glass beads (non-adh: 27% lysis vs. adh: 16%; $p<0.05$) suggesting that they were neither B-cells nor macrophages. They also possessed Fc-receptors by the criteria of EA monolayer enrichment (FcR+: 45% lysis vs. unfrac: 28%; $p<0.01$). These nonadherent cells were not depleted by utilizing a specific αT-cell Ab+C' (T depl: 42% lysis vs. non-T depl: 27%; $p<0.04$).

In summary, these studies suggest that αTBMA can act as an informational bridge between tubular antigens and what appear to be natural killer cells.

GLOMERULAR PATHOLOGY OF LATE-ONSET NEPHROPATHIC CYSTINOSIS WITH MASSIVE PROTEINURIA.
R.C. Pabico, M.F. Bryson, B.A. McKenna, B.J. Panner. Departments of Medicine, Pediatrics and Pathology, Univ. of Rochester Medical Center, Rochester, N.Y.

The nephropathic form of cystinosis is usually expressed clinically by renal tubular dysfunctions. Proteinuria, though a common finding, is usually minimal and of the "tubular" type. Three siblings (2 boys aged 18 and 13, a girl aged 11) with late-onset or adolescent cystinosis, whose renal features include proximal and distal tubular abnormalities and massive proteinuria (15, 14, 2 gm/day) at the time when their glomerular filtration rate was normal or modestly impaired (40, 100, 140 ml/min, respectively), had renal biopsy to define the glomerular lesions. There were no clinical or serological evidence for immune-complex disease. The glomerular lesions are: a) light microscopy: polykaryocytosis of epithelial cells, endocapillary foam cells, segmental mesangial hypercellularity, segmental sclerosis and capsular adhesions b) electronmicroscopy: varying degrees of endothelial and mesangial proliferation, segmental thickening and reduplication of basement membrane, fused epithelial foot processes, dissolved cystine crystals, no electron-dense deposits c) immunofluorescent microscopy: finely granular, irregularly distributed deposits of C3 and IgM in 2 patients, and only C3 in one. The light and electronmicroscopy findings are similar to those of the infantile form of cystinosis. The immunofluorescent findings, which have not been described in cystinosis, suggest that an immunologic mechanism may play a role in the causation of glomerular lesions of a disorder that primarily affects the renal tubules.

IgA/IgG KIDNEY DEPOSITS IN IgA NEPHROPATHIES; THEIR RELATIONSHIP TO CIRCULATING IMMUNE COMPLEXES.
T.M. Phillips*, S. Dosa*, A. Abraham*,B.N. Garrett* N.C. Kramer, A.E. Parrish and A.M. Thompson. Path. Dept., Georgetown Univ. Hosp. and Div. of Nephrol., George Washington Univ. Med. Ctr., Washington, D.C.

This study demonstrates a relationship between circulating immune complexes (CIC) and the IgA/IgG mesangial deposits, shown by immunofluorescence, in the glomeruli of 3 patients with different forms of glomerulonephritis (Henoch-Schonlein nephritis, Lupus nephritis and Mesangial proliferative GN). CIC were detected by C1q solid-phase and Raji cell assay. They were isolated on a weight basis by polyethylene glycol (PEG) precipitation/sedimentation, dissociated in acid and the components analysed. Frozen sections of the renal biopsies were also acid eluted and the components analysed. The PEG studies showed the presence of several CIC including a 19S complement-binding, platelet aggregating complex in all patients, but when compared to the tissue elutions only a 40-44S heavy IgA/IgG CIC was deposited. This complex contained a subclass of IgA and an IgG which was reactive against this IgA but not reactive against other autologous IgA subclasses or IgA from other patients. The IgA from both the CIC and the tissue elution showed a line of identity when reacted against the IgG from the CIC and the IgG from the tissue deposition. Both IgG's were identical in their reactivity against the IgA but were not rheumatoid factor positive or reactive against IgA secretory piece.

In conclusion, these findings show that only the IgA/IgG CIC were deposited in the mesangium and indicate the need for multiple CIC assays combined with tissue elution studies to identify and analyse the composition of pathogenic CIC.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS ASSOCIATED WITH WALDENSTROM'S MACROGLOBULINEMIA: ULTRASTRUCTURAL EVIDENCE OF IMMUNE COMPLEX DEPOSITION. Alan V. Richman and Victor Arean*. University of South Florida College of Medicine, Department of Pathology, Tampa, Florida.

Renal dysfunction in Waldenstrom's macroglobulinemia(WM) is relatively unusual although immunoglobulin light chains may be found in the urine in 30-40% of cases. We are reporting the clinical and pathologic features of an unusual patient with membranoproliferative glomerulonephritis associated with WM. Light microscopy revealed marked mesangial proliferation, lobular accentuation, and diffuse capillary wall thickening. Within some glomerular capillaries were voluminous, eosinophilic, intracapillary deposits, a previously reported characteristic feature of glomerular involvement in WM. Electron microscopy revealed large electron dense subendothelial and mesangial deposits characteristic of immune complex disease. Amorphous electron dense material, corresponding to the intracapillary deposits observed by light microscopy, was distinct from the subendothelial deposits. It has previously been proposed that glomerular involvement in WM was secondary to the passive deposition of circulating IgM concentrated in the glomerular capillaries by ultrafiltration (Morel-Maroger et al, N. Eng. J. Med. 283:123-129, 1970). This hypothesis was made without the benefit of electron microscopic data. While this mechanism may be operative, our ultrastructural observations suggest an alternative etiology - the glomerular deposition of immune complexes. The nature of the immune deposits needs to be clarified by the study of additional patients with glomerular disease associated with WM.

● UNIQUE EFFECT ON GLOMERULAR PERMEABILITY OF $F(ab')_2$ AND Fab' ANTIBODY (Ab) TO RAT PROXIMAL TUBULAR EPITHELIAL ANTIGEN (Fx1A). D.J. Salant, N.Capparell*, M.P. Madaio*, C.Darby*, M.M. Stilmant and W.G. Couser. Boston University Medical Ctr., Boston,MA.

Rats injected with anti-Fx1A IgG develop subepithelial immune deposits (SIDs) and Complement (C)-dependent, neutrophil-independent proteinuria after 5 days but no immediate proteinuria. In contrast, $F(ab')_2$ and Fab' prepared from the same anti-Fx1A produced immediate proteinuria ($F(ab')_2$ 43±7; Fab' 10±3; IgG 2.2±.3 mg/d). C3 depleted rats developed immediate proteinuria after $F(ab')_2$ Ab (63±16 mg/d) but not after an equimolar dose of whole IgG Ab (1.6±1.1 mg/d), while glomerular binding of ^{125}I Ab fragments was significantly less than that of equimolar doses of Ab IgG ($F(ab')_2$ .11±.01; Fab' .03±.01; IgG .17±.01, % administered dose). Proteinuria due to Ab fragments was transient (24-72 hr), non-selective and contained <10% injected Ab fragments. No proteinuria resulted from injection of equal amounts of non-Ab $F(ab')_2$ or Fab' fragments. IF showed faint, diffuse, glomerular capillary wall deposits of $F(ab')_2$ and Fab' after 24h which became granular with time and tubular brush border staining. SIDs with focal foot process effacement were seen by EM. Light microscopy and colloidal iron staining were normal.

Small amounts of glomerular bound $F(ab')_2$ and Fab' anti-Fx1A Abs alter glomerular permeability soon after fixation while larger quantities of whole IgG Ab do not. The glomerular lesion closely resembles C-independent anti-GBM nephritis, although anti-Fx1A Ab fragments bind to a different antigen at a different site in the capillary wall. Nephritogenicity of Fab' Ab excludes lattice-forming immune complexes in this process.

● CORRELATIONS BETWEEN SEROLOGIC FEATURES AND GLOMERULAR PATHOLOGY IN SYSTEMIC LUPUS ERYTHEMATOSUS(SLE). Jimmy L. Roberts, Alfredo Mocarquer,* and Edmund J. Lewis, Rush Medical College, Chicago, Illinois.

The membranous(MGN) and diffuse proliferative (DPGN) types of glomerulonephritis are major histologic variants in SLE. We have studied several immunologic parameters in serum and cryoprecipitable (Cr) immune complexes(IC) of SLE patients(6 MGN, 6 DPGN) in order to determine whether variations in the biologic properties of free anti-DNA(αDNA) antibodies(AB) and αDNA bound in CrIC correlate with the severity of glomerular inflammation. Cryoprecipitable immunoglobulin(Ig) and bound αDNA content were not different between MGN and DPGN; however, in vitro complement fixation(CF) by Cr αDNA was greater in DPGN(6/6 DPGN vs 0/6 MGN). This correlated with the finding that DPGN CrIC contained more C1q, C4, C3 and β1H globulin than did MGN($p<0.05$), and total Cr protein concentrations were higher in DPGN(184 vs 91 μg/ml, $p<0.05$). Similarly, DPGN had higher levels of serum IC measured by solid phase C1q(105 vs 46 μg/ml, $p=0.06$). DPGN was associated with significantly more free serum IgG anti-native DNA(*C. luciliae*, $p<0.002$) and DNA binding(Farr, $p<0.001$). Using a modified DNA binding assay, DPGN sera exhibited spontaneously precipitating(SP) αDNA(3/6 DPGN vs 0/6 MGN). Polyethylene glycol precipitation of IC removed SP αDNA. We conclude that several parameters differentiate DPGN from MGN: 1) DPGN has more free serum αDNA than does MGN. 2) SP αDNA, which appears to represent Ab-excess IC, is demonstrable in DPGN but not MGN. 3) While bound αDNA in CrIC are comparable, immune-bound CF αDNA is characteristic of DPGN but not MGN. The presence or absence of CF αDNA may explain inflammation in DPGN and the bland nature of MGN.

● PERSISTENT IMMUNE DEFICIENCY IN IDIOPATHIC NEPHROSIS DURING THE NEPHROTIC SYNDROME AND REMISSION. Gene Seligson, Umrana Ahmed*, Arvind Grover*and Kurt Lange. Lenox Hill Hosp., Renal Section, Dept. of Med. and New York Med. Coll., Renal Serv., New York, N.Y.

Patients with idiopathic (lipoid) nephrosis with or without a nephrotic syndrome have an immune deficiency documented by absence or abnormally low antibody titers to Endostreptosin (ESS), a cytoplasmic antigen of group A streptococci, ASLO, and Streptozyme. Antibodies to ESS, Streptolysin and Streptozyme were absent or depressed during the nephrotic syndrome and in complete remission (up to 20 years) in 34 children and 19 adults compared to 286 age and sex matched controls ($P<0.01$). In 20 patients with a nephrotic syndrome of other systemic diseases, antibody titers were in the range of controls. Urinary excretion of antibodies, as well as immunodepressant substances in serum have been excluded, the latter by crossover studies. Rapid antibody catabolism remains a remote possibility. Biopsies of nephrotic patients assumed to have idiopathic nephrosis but with normal streptococcal antibody titers, revealed a nephropathy of other systemic diseases. These tests may predict failure of prompt response to steroid therapy.

EFFECT OF INTRARENAL PERFUSION OF LYMPHOKINE ON GLOMERULAR HISTOLOGY IN THE RAT. Robert J. Shalhoub, Mary B. Jefferson,* Emory L. Rollins,* Vera L. Williams,* and Lucy D. Antoniou. Dept. of Med., VA Med. Ctr. and Georgetown Univ. School of Med., Washington, D.C.

It has been postulated that glomerular polyanion prevents albuminuria by providing an electrostatic barrier to the passage of these anionic proteins and that it also prevents pedicel fusion. It has also been postulated that lipoid nephrosis may be mediated by product(s) of activated T-cells by a direct effect on the glomerular capillary wall. We therefore examined the effects of acute intrarenal perfusion of unconcentrated lymphokine-rich lymphocyte supernatants upon the kidneys of Sprague-Dawley rats. Supernatants known to contain macrophage inhibitory factor (MIF) were perfused into isolated kidneys for 45-60 min. in 6 experiments. In 6 control studies, the perfusate consisted of culture medium alone (RPMI 1640) or Krebs-Ringer buffer containing 4% bovine serum albumin. The kidneys were then examined under light microscopy for glomerular polyanion by colloidal iron staining, and under electron microscopy for pedicel fusion. There was no clear-cut difference in glomerular uptake of colloidal iron or ultrastructure between control and experimental kidneys. We conclude that acute exposure of rat glomeruli to a MIF-containing lymphokine mixture has no detectable histological effect on glomerular polyanion or pedicels.

PATTERNS OF IMMUNE RESPONSE TO HEPATITIS B VIRUS (HBV) IN HEMODIALYSIS (HD) PATIENTS AND STAFF. JE Sherlock and E Ilamathi,* Department of Medicine, Nassau County Medical Center, East Meadow, New York. Meadow, New York.

Fifty-six HD patients and 26 staff were tested > 6 months after HBV infection. The presence of hepatitis B surface antigen (HB_SAg), antibody to surface antigen (anti-HB_S), and antibody to core antigen (anti-HB_C) was determined by radioimmunoassay in serum and cryoprecipitates (CPT). Cellular recognition (CR) of HB_SAg was tested by the antigen stimulated rosette forming assay with lymphocytes from the same sample. No staff had serum HB_SAg. Other responses among patients and staff did not differ and are combined according to serologic markers. CR among groups is compared as follows:

(1) 7 HB_SAg in serum and CPT, negative CR.
(2) 39 serum HB_SAg negative and anti-HB_S or anti-HB_C positive.
  (A) 15 CPT positive (4 HB_SAg positive, 11 anti-HB_S), 4 CR positive.
  (B) 24 CPT negative, 19 CR positive.
(3) 36 serum HB_SAg, anti HB_S, CPT negative, 4 CR positive.

A significant decrease in CR was noted in antibody positive individuals with surface antigen markers in CPT, and in HB_SAg carriers. Definition of cellular mechanisms is not possible from the data, but this type of grouping allows testing and comparison of specific cellular mechanisms in response to HBV and possibly to other initiators of immune complex disease.

● GLOMERULAR EPITHELIAL CELL (GEC) ENDOCYTOSIS OF PROTAMINE-HEPARIN AGGREGATES IN HEYMANN NEPHRITIS (AICN) AND PUROMYCIN AMINONUCLEOSIDE NEPHROSIS (PAN). Z. Sharon, M.M. Schwartz, B.U. Pauli*, and E.J. Lewis, Rush Medical College, Chicago, Illinois.

Protamine-heparin aggregates (PHA) which localize in the lamina rara externa (LRE) of the GBM are cleared by an active metabolic process which was identified as GEC endocytosis. As epimembranous accumulation of immune aggregates is the main feature in AICN, we evaluated GEC's capacity to clear PHA from the GBM at sites of immune aggregate accumulation in early AICN and compared it to GEC's clearance function in early PAN. Intravenous administration of protamine and heparin was followed by sequential renal biopsies. Using a computerized morphometric technique, PHA disappearance curves were calculated for 2 separate zones of the GBM in AICN: (I) normal appearing LRE: (II) above immune aggregates in direct apposition to GEC plasma membrane. These were compared to the curves calculated for PAN. In Zone I of AICN clearance of PHA proceeds according to first order kinetics, similar to that in normal animals. By contrast, Zone II AICN curves show accumulation of PHA rather than clearance. After 3 hours 169.4% of baseline PHA were present in Zone II of AICN, while 34.6% remained in Zone I ($P<.01$) and 19.5% in PAN ($P<.01$). There was no significant difference between Zone I of AICN and PAN. We conclude: (1) Protamine-heparin aggregates which localize at sites of immune aggregate accumulation in early AICN are not cleared and actually accumulate at 3 hours. (2) At this early stage of PAN, the GEC retain their normal clearance function. (3) Impairment of GEC clearance function may contribute to immune aggregate accumulation in AICN.

● IMMUNE ABNORMALITIES IN IgA NEPHROPATHY (BERGER'S DISEASE). I. Stachura, G. Singh* and T.L. Whiteside*. Univ. of Pittsburgh, Dept. of Pathology and Allegheny General Hospital, Pittsburgh, Pa.

Thirteen patients with IgA nephropathy confirmed by renal biopsies were studied for evidence of disordered immune mechanisms. Circulating immune complexes (CIC) were determined by agarose gel zone electrophoresis (AGE) and Raji cell radioimmunoassay (RIA). Serum levels of immunoglobulins (Ig) G,A,M, of C3, C4 and properdin factor B (PFB) were measured by the rate nephelometry. Tissue studies included fluorescent, light and electron microscopy, staining for intracellular Ig and lysozyme by immunoperoxidase (IP) and determination of glomerular C3 receptors (C3R) by EAC rosettes. CIC were detected in 54% of patients by AGE; in 31% by Raji and in 69% by both methods. CIC contained IgG and not IgA. Serum IgA was elevated (>2SD) in 46% of patients and IgM and PFB were also increased in some patients (20%). Serial determinations showed persistence of Ig abnormalities and trasiency of CIC. No serum C3 or C4 abnormalities were detected. In the glomeruli, mesangial deposits of IgA, IgG, properdin and C3 were present. C3R available for EAC binding to glomerular cells were decreased. The number of IgA-producing lymphoid cells in renal interstitium of our patients was increased as compared with other glomerulonephritides. Lysozyme-containing cells were not detected. Elevated serum IgA and the presence of numerous IgA-producing cells in the renal tissue may reflect an abnormality in IgA immunoregulatory mechanisms. Aggregated IgA localized in the mesangium could contribute to the pathogenesis of renal disease due to its inhibitory effect on the clearance of nephrotoxic IgG-containing immune complexes.

● GLOMERULAR HANDLING OF IMMUNE COMPLEXES IN MALARIAL GLOMERULONEPHRITIS OF RATS. R.B. Sterzel, J.H. Ehrich*, H.Lucia*, M.Perfetto*, M.Kashgarian. Yale Univ.Sch.of Med.-VA Med. Center, New Haven, CT.

The disposal of glomerular immune deposits and the participation of infiltrating monocytes were studied in acute malaria-associated glomerulonephritis (GN). Young Sprague-Dawley rats were infected with Plasmodium berghei. Parasitemia reached a maximum between day 9 and 12, ending by day 16. Circulating immune complexes rose transiently above control levels at this time. GFR remained normal but urinary protein excretion increased significantly between day 8 and 16. In all infected rats, renal immunofluorescence microscopy (IFM) showed diffuse granular deposition of rat IgG,IgM and C3 in a mesangial distribution. The staining was strongest on day 10, then diminished and disappeared after day 32. Electron dense deposits were not seen before day 14 when they became detectable in the mesangial matrix along the inner aspect of the glomerular basement membrane. They were more conspicuous on day 21 and disappeared by day 60. Transient glomerular hypercellularity was documented on day 10 (mean 52.9 ± 4.8 SD nuclei/tuft vs. controls 41.6 ± 2.8; $p < 0.005$). This was associated with a scanty monocytic infiltrate reaching maximal counts of α-naphthol-butyrate esterase-positive monocytes on day 10 (mean 2.9/tuft, range 0-5, vs. controls 0.2, range 0-1). The results indicate: (1) elimination of glomerular immune deposits in malarial GN of rats involves their gradual condensation and degradation in the mesangium which reduces detection by IFM while leading to formation of transient electron dense deposits; (2) the glomerular injury is mild when deposited immune complexes can be disposed of in the mesangium without participation of a sizeable monocytic infiltrate.

MALEIC ACID PRODUCES NECROSIS IN RAT PROXIMAL TUBULES. Regina Verani, Eileen Brewer, Ruth Bulger. Ann Ince and Jerry Gibson. Univ. of Tex. Med. Sch., Depts. of Path. & Ped., Houston, Texas.

Administration of maleic acid to rats is used as an experimental model of Fanconi's syndrome. Although effects of maleic acid have been described mainly in proximal tubules, some studies have suggested important distal tubular involvement as well. We studied rats which received maleic acid (200mg/kg/hr or 400mg/kg/hr) IV over one hour and were then perfused with Karnovsky fixative either immediately (4 rats) or 24 hours later (4 rats). Four control rats received saline without maleic acid. Morphology of the kidneys was studied by LM, TEM and SEM. In kidneys of rats studied immediately after maleic acid, 50% of the proximal tubules had numerous vesicles and mitochondrial alterations. A few necrotic tubular cells were seen in 2 of 4 rats. In kidneys studied at 24 hours, proximal tubules in the medullary rats were completely necrotic, proximal tubules in the outer stripe (P_3M) were extensively necrotic ($62.5\pm15.9\%$, sem) and some P_2 convoluted segments were focally necrotic. Changes were no different with the 200mg or 400mg dose. Distal convoluted tubules contained prominent casts, but no necrosis was observed. Collecting ducts demonstrated significantly increased numbers of dark cells both immediately after and at 24 hours after maleic acid ($p<0.005$ and $p<0.025$ in outer and inner stripes, respectively, as compared to controls). We conclude that maleic acid at these dosages produces necrosis only in the proximal tubules, especially those in the medullary rays. The increase in dark cells may represent some adaptive response of the collecting duct to renal injury caused by maleic acid.

● A STUDY OF IMMUNE COMPLEXES IN A RENAL ALLOGRAFT WITH DE NOVO MEMBRANOUS NEPHROPATHY. T. Sugisaki*, J. R. Brentjens*, K. Kano*, G.A. Andres, S.Anthone and F. Milgrom*. Departments of Microbiology, Pathology, and Surgery, State University of New York at Buffalo, Buffalo, New York 14214

In our previous studies, circulating immune complexes (IC) were detected by antiantibody (AA) inhibition tests in the sera of some patients with long-term renal allografts. AA adsorption test have demonstrated IC deposited in rejected grafts.

A 20 year old female patient suffering from chronic renal failure due to focal glomerulosclerosis received a renal allograft which was removed 2 years later. Immunopathological studies of the graft showed interstitial infiltration of mononuclear cells and diffuse thickening of glomerular capillary walls due to subepithelial immune deposits (ID) of IgG and C3.

The ID were stained with anti-IgM conjugate after incubation of the section with AA, indicating IC nature of the deposits. Dissociation of the IC in the sections by various soluble antigens were then attempted. For this purpose, solubilized HLA antigens, renal tissue extracts of various species and some fractions of plasma proteins of several species were used. The ID were completely dissociated by incubation of the section with human γ-globulin (commercial preparation, FII, 1 mg/ml) or heat aggregated human γ-globulin (FII, 0.1 mg/ml), but not by any other antigens employed. Fresh normal sera of human and animal origin or native and heat aggregated γ-globulin of rabbit and sheep failed to dissociate the ID.

These results suggest that the ID contain IC of IgG rheumatoid factor and the denatured IgG.

● ROLE OF ELECTRICAL CHARGE IN THE PATHOGENESIS OF EXPERIMENTAL MEMBRANOUS NEPHROPATHY. Harry J. Ward,* Elaine S. Kamil,* Arthur H. Cohen, and Wayne A. Border. Depts. of Medicine & Pathology, Harbor-UCLA Medical Center, Torrance, CA.

In order to examine the role of electrical charge as a determinant of glomerular immune complex formation we induced chronic serum sickness nephritis in rabbits with injections of cationic (pI 9.5-10.1), anionic (pI 3.5-4.6) and native (pI 4.5-5.1) bovine serum albumin (BSA). The BSAs were shown to be comparable in molecular size, immunogenicity and disappearance time from the circulation. Groups of New Zealand white rabbits received daily 50 mg intravenous injections of the respective BSA for 6 weeks. At 2, 4 and 6 weeks renal biopsy was performed and BUN and albuminuria were measured. Additional groups received daily low dose injections of 1, 10 or 25 mg of each BSA.

Rabbits receiving cationic BSA uniformly developed heavy granular capillary wall deposits of IgG, C3 and BSA detected at 2 weeks and increasing until 6 weeks. Animals injected with low dose cationic BSA developed similar lesions. In contrast, rabbits receiving anionic or native BSA formed mainly mesangial deposits at 2 and 4 weeks with capillary wall deposits appearing at 6 weeks. Ultrastructural examination of animals receiving cationic BSA revealed pure, extensive formation of epimembranous deposits, whereas such deposits were absent or rare in animals injected with anionic or native BSA. Albuminuria, but not azotemia, was greater at all times in the cationic groups. Single and paired label perfusion studies in nonimmunized animals showed direct renal binding of cationic BSA. These experiments demonstrate the reproducible induction of epimembranous deposits by an exogenous cationic antigen and suggest a mechanism by which antigenic charge can predispose to in situ immune complex formation and membranous nephropathy.

● ABROGATION OF IMMUNE GLOMERULONEPHRITIS (GN) IN RABBITS BY ANTI-MACROPHAGE (M) SERUM. Stephen R. Holdsworth,* T. James Neale,* and Curtis B. Wilson. Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California.

Large numbers of M were found by glomerular cell culture and morphologic techniques in glomeruli of rabbits with acute serum sickness (AcSS) and with a passive autologous phase model of anti-GBM antibody-induced GN (PAGBMN). To determine the role of M in the glomerular injury, rabbits were treated with sheep anti-rabbit macrophage serum (AMS) or control normal sheep serum (NSS). NSS administration had no effect on either model of GN. AMS reduced the number of circulating monocytes without affecting polymorphonuclear leukocytes (PMN) and prevented the accumulation of M within glomeruli in both models (AcSS/NSS $\bar{x}$ 126 per glomerulus; range 40-251; AcSS/AMS $\bar{x}$ 8; range 1-44; PAGBMN/NSS $\bar{x}$ 52; range 27-69; PAGBMN/AMS $\bar{x}$ 5; range 2-7). The AMS treated rabbits had a profound reduction in histologic changes of GN and in proteinuria (AcSS/NSS mean 516 mg per 24 hrs; range 200-991; AcSS/AMS mean 41; range 3-161; PAGBMN /NSS mean 335; range 55-975; PAGBMN/AMS mean 10; range 2-24). Complement depletion with cobra venom factor did not affect the development of GN nor the number of glomerular M in either model. Similar studies in the heterologous phase anti-GBM GN revealed no effect of the AMS on this PMN related phase of injury, demonstrating the selectivity of the antiserum. Prevention of glomerular M accumulation can largely prevent AcSS and PAGBMN in rabbits, implicating M as a major mediator of glomerular injury and consequent proteinuria in these models.

● FIXATION OF ANTI-FIBRONECTIN (FN) ANTIBODIES IN THE RAT MESANGIUM IN VIVO. Maurizio Zanetti,* and Tsuyoshi Takami,* (intr. by F.W. Spong). UCHC, Dept. of Pathology, Farmington, Connecticut.

Fibronectin (FN), a 450,000 dalton plasma glycoprotein, is present in the normal kidney mainly in the mesangial area. In an attempt to elucidate whether antibodies (Ab) to FN would localize in the mesangium, we injected Fischer rats with rabbit IgG anti-FN (10 mg/100 gm) directed against rat plasma FN. Immunofluorescent (IF) examination at 24 hrs showed a diffuse mesangial deposition (MD) of rabbit IgG in all rats (n=10) given anti-FN Ab. From day 10, autologous IgG but not C3 was also seen. Blockade of the reticuloendothelial system by i.v. administration of colloidal carbon (c.c.) before the injection of anti-FN Ab resulted in more persistent MD in all rats (n=9). No MD were seen in control rats given preimmune Ig (n=5), normal rabbit IgG without (n=5) or with c.c. (n=5). By light microscopy, no definite glomerular abnormalities were found on day 20. No significant proteinuria occurred in rats with MD.

Experiments performed to exclude a passive mesangial uptake of FN-anti-FN immune complexes showed that injection of ^{125}I-FN prior to administration of anti-FN Ab did not result in a significant renal uptake of ^{125}I-FN in rats given anti-FN Ab as compared to rats given normal rabbit IgG (0.06 ± 0.02 vs 0.06 ± 0.01% at 45 min and 0.32 ± 0.12 vs 0.45 ± 0.13% at 4 hrs).

Our results indicate that (1) anti-FN Ab localize in vivo within the mesangium, and (2) the initiating phase of immune complex formation is due to a direct "in situ" fixation of anti-FN Ab.

● INCREASED ALTERNATIVE COMPLEMENT PATHWAY PROTEIN LEVELS IN IGA NEPHROPATHY. R.J. Wyatt, B.A. Julian,* R.G. McMorrow and J.H. Galla. University of Kentucky Medical Center, Dept. of Medicine and Pediatrics, Lexington, Kentucky.

Serum levels of complement component and control proteins were determined in adult patients (pts) with IgA nephropathy with normal renal function since onset of disease (14), impaired function at diagnosis (7) or initial normal function with subsequent deterioration (5). In normal circumstances serum levels of alternative pathway (AP) component proteins, C3 and Factor B are dependent upon those of their control proteins, βlH and C3b inactivator (C3bINA). In pts maintaining normal function, mean levels of AP proteins were increased compared to healthy adult mean for C3 (163mg% to 141mg%, $p < 0.001$), Factor B (281μg/ml to 241μg/ml, $p < 0.05$), βlH (644μg/ml to 561μg/ml, $p < 0.001$) and C3bINA (46μg/ml to 40μg/ml, $p < 0.01$). Pts with renal failure secondary to IgA nephropathy had low normal levels of AP proteins regardless of status (chronic renal failure—6, dialysis—3, functioning transplant—3).

Mean C4 and C9 levels were elevated in pts with normal or impaired function. Mean levels of Clq, C2, Cl-inhibitor, C5, C6, C8 and properdin did not differ significantly from healthy adult mean in pts with normal or abnormal function. Present study does not provide a mechanism for increased complement protein levels. A possible explanation for increased levels of βlH and C3bINA in stable pts is that these proteins might function to dampen potential AP activation, either systemic or intra-glomerular, and increased levels may prove to be protective against development of progressive disease.

MODIFICATION OF PROGRESSIVE RENAL ABLATION NEPHROPATHY IN THE RAT BY ANTIPLATELET AGENTS. Stephen W. Zimmerman and Jeff VanStelle*. University of Wisconsin, Dept. of Medicine, Madison, Wisconsin.

Ablation or infarction of > 5/6's of renal mass produces a progressive nephropathy associated with hypertension and uremia. Fibrinogen and platelets may be seen in glomeruli, and amelioration with heparin has been reported. The present study was done to assess the effect of antiplatelet agents Aspirin (ASA) and dipyridamole (D) in rats with uni-nephrectomy and ligation of both poles of the remaining kidney. Rats were fed a control diet or a diet containing ASA 5 mg, 10 mg, 20 mg or 40 mg/day or D 20 mg or 40 mg/day. Rats were studied at 5 weeks. Mean results are tabulated.

Group	N	BP mmHg	Heart wt/ 100 gm rat	BUN mg/dl	Urine Protein mg/day
Control	12	141±4	401±15	74±8	79±11
ASA-5	5	122±6*	379±11	51±7	68±12
ASA-10	10	124±2*	341± 6*	38±4*	41± 4*
ASA-20	6	119±9*	381±10	73±5	68±12
ASA-40	7	131±8	410±20	79±7	91±17
D-20	8	119±6*	340± 6*	39±2*	58± 6
D-40	10	120±4*	349±11*	51±6*	72±12

*Significantly different from control

Compared to controls, rats fed ASA 10 mg/day and D-20 or 40 mg/day had fewer abnormal glomeruli and less severe interstitial fibrosis and arteriolar hypertrophy. Additionally fewer glomeruli had deposits of fibrinogen; albumin and IgG. It is concluded that ASA 10 mg/day and D at 20 and 40 mg/day reduced BP, heart weight, BUN and renal histopathologic alterations. ASA in larger doses was ineffective. The mechanism of action of low dose ASA and D could be through their effect on platelets.

Pathophysiology

PARATHYROID HORMONE (PTH) AND GLUCOSE (G) INTOLERANCE IN UREMIA. M. Akmal,* D.A. Goldstein, S. Multani,* and S.G. Massry. Div. Neph., Dept. Med., USC School of Medicine, Los Angeles, CA.

Evidence has accumulated suggesting PTH is a uremic toxin. This study examines role of PTH in genesis of G intolerance in uremia. Changes in blood G (mg/dl) and insulin (I, mU/ml) were measured frequently for 60 min after IV G (IVGTT) and K-g rates (%/min) were calculated before and after 3 months of comparable uremia produced by 5/6 nephrectomy in 6 pairs of dogs. Half were parathyroidectomized before uremia (TPTX; Ccr from 57±2.2 to 14±4.5 ml/min) while in others the glands were not removed (Control; Ccr from 56±2.1 to 11±3.4 ml/min). Fasting blood G was not different among the two groups both before and after uremia while blood I was higher ($p<0.01$) in uremic controls (24.7±2.6) than in TPTX (17.9±1.2). Controls had G intolerance after uremia and blood G after IVGTT remained higher ($p<0.01$) than before uremia. In contrast, blood G curves after IVGTT before and after uremia in TPTX dogs were identical. K-g rate fell after uremia from 2.9±0.48 to 1.2±0.18 ($p<0.01$) in controls but remained unchanged in TPTX dogs (2.4±0.43 vs 2.9±1.4). Blood I in TPTX dogs after IVGTT were 2-3 times higher than in controls. For any given level of blood G, I levels were higher in TPTX than controls. Blood I fell rapidly in TPTX dogs and returned to normal by 60 min while I remained elevated in controls. Data show: 1) glucose intolerance does not develop in uremia in absence of PTH, 2) PTH affects I release in uremia, 3) higher I levels in TPTX dogs overcome insulin antagonism resulting in normal G tolerance, and 4) rapid fall in blood I is consistent with increased utilization of I by skeletal muscles.

GENTAMICIN (GM) STIMULATION OF CONCENTRATIVE TRANSPORT OF PAH. Vicihi Batuman, and Richard P. Wedeen VA Medical Center, E. Orange, N.J.

We have used a new technique of combined section freeze-dry autoradiography and immunofluorescent microscopy to examine, simultaneously, the distribution of GM and PAH in rat kidneys. GM, 100 mg/kg, was administered intraperitoneally to rats for 2 days and cortical slices prepared 48 hrs after the first injection. Slice uptake of PAH-3H was measured after incubation in vitro in buffer containing 0.05 mM PAH-3H. Autoradiographs were treated with rabbit anti-GM antibody and stained with fluoresceinated anti-rabbit IgG. The PAH-3H S/M ratio was increased significantly (50% or more) compared to control slices only after incubation for more than 120 min. Combined immunofluorescent microscopy and section freeze-dry autoradiography demonstrated PAH-3H and GM always together in about 2/3 of proximal tubule (PT) segments. The remaining PT segments showed an absence of PAH-3H and GM but did not appear damaged by light microscopy. GM-3H was found in a similarly limited portion of PT segments by combined immunofluorescence and autoradiography 6 hrs after in vivo injection of 100 mg/kg GM-3H. These findings indicate that stimulation of PAH uptake by GM is confined to a limited portion of the PT. Cellular accumulation of GM and stimulation of PAH uptake occur in the same segments of the PT. Since GM stimulation of PAH uptake was not evident after less than 120 min of slice incubation, enhanced PAH uptake appears to be the result of efflux inhibition at the peritubular membrane in affected PT segments.

THE INTESTINAL PROFILE OF Na-K-ATPase in ACUTE RENAL FAILURE. Abraham Aviv, Burton P. Fine*, and Tatsuharu Kobayashi*. New Jersey Medical School, Div. of Ped. Nephrol., Newark, New Jersey.

In previous studies we demonstrated that induction of acute renal failure (ARF) by bilateral nephrectomy (BN) in the rat resulted in a reversal of the jejunal transport of potassium from absorption to secretion. This change occurred in concert with an increase in the specific activity of jejunal Na-K-ATPase. The present study focuses on the specific activity of the enzyme in various segments of the intestinal tract of Sprague-Dawley rats at time intervals following BN or sham operations (S). The activity of the enzyme was measured in the proximal 5-cm segments of the duodenum (D) and jejunum (J) as well as the distal 5-cm segments of the ileum (I) and colon (C). The enzymatic activity (m ± SEM) expressed in uMol Pi generated/mg protein/hr. is presented in the following table. By 22-24 hrs. following induction of ARF the duodenum and colon manifested an increase in the specific activity of Na-K-ATPase ($P<0.01$ and $P<0.05$ respectively). By 48-50 hrs. after induction of ARF all intestinal segments exhibited a highly significant surge in the specific activity of the enzyme ($P<0.01$).

	22-24 hrs.		48-50 hrs.	
	S	ARF	S	ARF
D	14 ± 0.8	20 ± 1.3	13 ± 0.8	17 ± 1.6
J	14 ± 0.8	17 ± 1.1	13 ± 0.7	18 ± 1.3
I	8.7 ± 0.8	9.3 ± 0.8	8.5 ± 0.6	12 ± 1.0
C	9.5 ± 1.0	13 ± 1.2	9.5 ± 1.1	18 ± 1.7

It is speculated that in this model of ARF the increase in Na-K-ATPase activity in the intestinal mucosa may relate to an augmented potassium excretion by the entire intestinal tract.

BODY FLUID COMPOSITION IN CHRONIC RENAL FAILURE. J Bauer and C Brooks*, VA Hosp. and Dept. Medicine, Univ. MO. Medical Center, Columbia, Missouri.

Studies were performed to assess body fluid composition alterations occurring in 10 patients undergoing chronic hemodialysis. Plasma volume (PV) by ^{125}IHSA, extracellular fluid volume (ECF) by $Na_2{}^{35}SO_4$, and total body water (TBW) by ^{3}H were assessed 24 hrs following hemodialysis to dry weight (Day 2), following infusion of normal saline to increase body weight by approximately 2 kg (Day 3), and following hemodialysis to decrease body weight by approximately 2 kg (Day 5). Mean results are indicated below:

	PV (L)	ISF (L)	ECF (L)	ICF (L)	TBW (L)	Wt (kg)
Day 2	3.4	9.5	12.8	17.8	30.6	62.1
Day 3	4.0	11.1	15.1	17.7	32.6	64.4
Δ	+0.6‡‡	+1.6‡‡	+2.3‡‡	-0.1	+2.0†	+2.3‡‡
Day 5	3.9	9.5	13.4	17.7	30.6	63.0
Δ	-0.1	-0.6‡‡	-1.7‡‡	0.0	-2.0†	-1.4‡‡

†$p<0.025$, ‡‡ $p<0.005$ compared to previous day.

TBW constituted from 48.5 to 51% of body weight. ECF constituted from 41.8 to 46.3% of total body water. Salt and water alterations (normal saline infusion and ultrafiltration) were restricted to the ECF component of TBW. In the ECF it was principally the interstitial fluid (ISF=ECF-PV) that buffered salt and water expansion or depletion. There was no evidence for volume alterations in the intracellular fluid (ICF=TBW-ECF). We conclude that the ISF is the buffer zone which maintains the proper balance and relationship between vascular capacity and volume. Serial measurements of plasma renin activity and aldosterone demonstrated elevated levels, especially under conditions of PV contraction, which suggests activation of this system in an attempt to maintain/support total blood volume homeostasis.

GLOMERULAR HEMODYNAMICS IN AGED RATS. B. Booker* and R. Williams. The Univ. of Alabama in Birmingham, Dept. of Med., Birmingham, Alabama.

Previous micropuncture studies in immature and mature rats suggest that whole kidney (GFR) and single nephron glomerular filtration rate (SNGFR) increase in parallel with growth and maturation. The increase in SNGFR is thought to be a result of an increase in glomerular plasma flow (GPF) and the glomerular ultrafiltration coefficient (Kf). The importance of age matched controls in studying long-term pathologic states promoted our studies in male Sprague Dawley rats at 3 mos., 9 mos. and 12 mos. of age. SNGFR was estimated from distal tubule collections; glomerular capillary pressure from stop flow pressure and afferent oncotic pressure; filtration fraction from efferent protein collection and proximal tubular pressure from direct micropuncture. Results are mean ± SEM.

Age mos	BW† gms	KW† gms	BP† mmHg	GFR ml/min	SNGFR nl/min	GPF nl/min	Kf nl/min.mmHg	EFP mmHg	RA mmHg/nl.min
3	360	1.5	106	1.0	35	86	1.69	21.9	.4
N=3	±22	±.1	±9	±.1	±1	±4	±.2	±3.4	±.1
9	672*	2.1*	135	1.6*	28	88	2.8	10.5*	.8
N=6	±17	±.1	±9	±.2	±5	±21	±.5	±1.2	±.2
12	624*	1.8	147*	.85*	18*	87	1.7	11.4	.7
N=4	±45	±.2	±6	±.14	±2	±16	±.2	±2.4	±.1

(*p<.05)

† BW - body weight; KW - kidney weight; BP - blood pressure; EFP - effective filtration pressure.

These results indicate that at 9-12 mos. SNGFR and GFR no longer increase with age, but begin to decline. The decrease in SNGFR is mostly the result of a marked increase in afferent arteriolar resistance (RA) with no significant change in GPF or Kf.

SEVERE HYPERCALCEMIA IN CHRONIC HEMODIALYSIS PATIENTS INGESTING THERAPEUTIC DOSES OF $CaCO_3$. D. A. Brown,* L.A. Hebert, W.H. Bay, J.B. Cornacoff* and R.A. Zager. Dept. of Med., Ohio State Univ., Cols.

$CaCO_3$ is widely used to control hypocalcemia and hyperphosphatemia in patients with chronic renal failure. However, $CaCO_3$ therapy alone is often insufficient to restore serum calcium levels to normal and thus it is necessary to add vitamin D preparations. The patients described in this report are remarkable because they developed striking hypercalcemia while ingesting only calcium carbonate in therapeutic doses. Underlying renal diseases were SLE glomerulopathy (pt A), unspecified chronic GN (pt B) and diabetic glomerulosclerosis (pt C). Duration on dialysis ranged from 2-6 yrs. Each patient received 1200mg of $CaCO_3$ tid for 5 days to 30 days before hypercalcemia was discovered. They received no other medications which are known to affect calcium metabolism. The table shows the range of fasting, predialysis serum calcium levels (mg/dl) observed:

Pt	Pre-$CaCO_3$	$CaCO_3$	Post-$CaCO_3$
A	9.4-10.1	12.8-14.1	9.5-9.6
B	9.8-10.0	12.1-14.1	9.5-9.8
C	8.8- 9.2	12.5-14.1	9.0-9.4

At peak serum calcium levels, pt A was grossly disoriented, pt B developed increased PVC's and pt C felt lethargic. iPTH (C-terminal) measured at peak hypercalcemia was 3x normal in pt A and 9x normal in pt B. Nevertheless, the hypercalcemia was clearly related to $CaCO_3$ ingestion since cessation of $CaCO_3$ resulted in return of serum calcium levels to normal within one week. We conclude that some chronic renal failure patients are inordinately susceptible to the calcemic action of $CaCO_3$. The mechanism is unknown but may be related to nonsuppressable secondary hyperparathyroidism.

DECREASED TESTOSTERONE PRODUCTION BY UREMIC RAT LEYDIG CELLS IN VITRO. G.R. Briefel, P.D. Tsitouras* S.M. Harman* and M.R. Blackman*. Dept. of Medicine, Baltimore City Hospitals and Gerontology Research Center, National Institute on Aging, Baltimore, MD

We have reported subnormal levels of serum testosterone (T), decreased in vitro T secretory response to hCG and reduced gonadotropin receptor number in Leydig cells from male uremic rats (Clin. Res. 28:256A, 1980). The present study was designed to elucidate this uremia-associated defect by investigating: 1) the time-course of in vitro Leydig cell T secretory response to hCG and, 2) intracellular mechanism(s) responsible for T hyposecretion.

Mature male Sprague-Dawley rats were made chronically uremic by 5/6 nephrectomy. Testes were digested with collagenase and Leydig cells separated from seminiferous tubules. T secretion by Leydig cells was determined after incubation with hCG (0.02-2.0 ng/ml) for 60, 120 and 180 min at 37 C. The dose response curves of uremic rats (n=6) were significantly different from controls (n=6), the uremic showing a response 5% (95% confidence limits 2-12%) that of controls at 60 min., 9% (4-19%) at 120 min., and 49% (31-72%) at 180 min. T secretion was also measured after incubation with dibutyryl cAMP (5-500 µg/ml) for 60 min; Leydig cells from uremic rats (n=5) showed a response 24% (9-64%) that of the controls (n=5).

Our data indicate that the T secretory defect in Leydig cells from uremic rats is partially reversed by prolonged exposure to hCG in vitro. Although the 48% reduction in the number of Leydig cell gonadotropin receptors could be partially responsible for the above defect, the dibutyryl cAMP data indicate that additional changes distal to adenylate cyclase activation also occur.

ROLE OF IMPERMEANT SOLUTES (IS) IN RECOVERY FROM NOREPINEPHRINE (NE)-INDUCED ACUTE RENAL FAILURE (ARF). T.J. Burke and R.W. Schrier. Dept. Med., Univ. Colo. Hlth. Sci. Ctr., Denver, CO.

It has been proposed that increased extracellular fluid (ECF) osmolality (OSM) may attenuate ARF by preventing cell swelling. Alternatively, the impermeant nature of the solute rather than its concentration may be the primary determinant of the protection from ARF. This hypothesis was tested by comparing the effect of hypertonic saline (HS), isotonic mannitol (IM) and isotonic polyethylene glycol (IPG) in prevention of NE-induced ARF. To avoid extrarenal factors, kidneys were flushed with one of these solutions prior to NE. HS did not prevent the fall in inulin clearance (CIn) at 3h compared to untreated control (C) kidneys (4 vs 3 ml/min, NS) in spite of the hyperosmolality (1400 mOsm/kg H_2O) of the intrarenal perfusate. In contrast, IM minimized the fall in CIn at 3h (15 vs 3 ml/min, p<.01) in spite of no change in ECF OSM of the renal circulation. To test if another isotonic IS could also protect, IPG was perfused. IPG also minimized the fall in CIn (18 vs 3 ml/min, p<.01). Proximal tubule (PT) micropressures at 3h did not correlate with protection. However, at 1h, before CIn can be accurately measured, C and HS kidneys which were not protected had significantly lower PT (C=13, HS=18 mmHg) compared to protected kidneys (IM=30, IPG=30 mmHg). These studies indicate that the impermeant nature of a solute rather than its effect on ECF OSM correlates best with protection from ARF. Protection is an intrarenal phenomenon; with the use of IS, the 1h rise in PT may flush debris from the nephron and prevent tubule obstruction rather than reduce cell swelling.

EFFECT OF CONVERTING ENZYME INHIBITION BY CAPTOPRIL (C) ON RENOVASCULAR RESPONSES DURING HEMORRHAGIC HYPOTENSION (HH) IN THE DOG. H. Canos and H. Fung, (introd. by A. Thomson), Dept. of Med., Univ. of Man. Renovascular response to graded HH and re-infusion (RI) of shed blood was studied in 3 groups of mongrel dogs. Graded HH was produced by bleeding 27 ml/kg over 8 ten-minute intervals. Hypovolemia was maintained for an additional 2.5 hours. Shed blood was re-infused in a similar graded fashion. RBF was measured using EM flowmeters. Group 1 (n=7) served as the control. In group 2 (n=8), C (1 mg/kg I.V.) was given before hemorrhage (Pre-H) and supplemental doses were given post-H and pre-RI. In group 3 (n=4), C was given post-H and pre-RI.

		BP(%)	RBF(%)	RVR(%)
Post-H	Gp 1	77.3	67.3	117.4
	Gp 2	59.7	60.5	105.2*
	Gp 3	69.4	68.8	111.7
Pre-RI	Gp 1	72.3	44.4	263.6
	Gp 2	57.7*	84.2*	78.5**
	Gp 3	59.7*	86.7*	94.8**
Post-RI	Gp 1	87.0	71.0	137.1
	Gp 2	77.7*	123.9*	70.1*
	Gp 3	88.3	108.6*	87.5*

(Data represent group means expressed as a percentage of the pre-H value). Persistent renal vasoconstriction occurred following prolonged HH and was not abolished with RI. However, in spite of lower BP, C given either pre-H or post-H resulted in higher RBF and lower RVR. Persistent renal vasoconstriction was abolished. Saralasin treatment resulted in similar hemodynamic changes. These findings suggest that the renin-angiotensin system plays a major role in mediating renal vasoconstriction during HH.

INITIATION PHASE OF CIS-DIAMMINEDICHLORPLATINUM (CP)-INDUCED ACUTE RENAL FAILURE (ARF) IN RATS. S. Chopra, J.S. Kaufman, D.Chase* and W. Flamenbaum. Renal Sections, Boston VA Medical Center and Lemuel Shattuck Hospital, Boston, MA.

CP (10 mg/kg,ip)-induced ARF has a prolonged initiation phase. In metabolic studies a concentrating defect characterized by low urine osmolality and urine to plasma (U/P) creatinine ratios was observed at 24 hr in rats who eventually developed established ARF. 25% of rats failed to develop either the concentrating defect or ARF, and the reasons for this are unclear. To evaluate this, rats were studied 6 hr after CP. Single nephron (SN) glomerular filtration rate (GFR), animal GFR, and U/P-Inulin (In) ratio, urine flow rate (V) at 6 hr and 48 hr after CP were:

	SNGFR nl/min	GFR ml/min/100gBW	U/P-In	V 1/min
Control	33.8	0.83	489	5.8
CP-6 hr	31.2	0.81	385[a]	6.7
CP-48 hr	24.4[a,b]	0.53[a,b]	274[a,b]	13.7[a,b]

Significantly different (P<0.05) from control (a) or 6 hour studies (b).

Proximal intratubular hydrostatic pressures were not significantly different from control at 24 hr and 48 hr. Proximal microinjection studies at 48 hr demonstrated "leak" of In. These studies indicate that the earliest CP-induced renal change is a concentrating defect, apparent at 6 hr, while SNGFR and GFR are well-maintained. SNGFR and GFR decrease at 48 hr, a time at which tubular fluid leak and tubular obstruction are also present. This indicates progression of CP-induced tubular damage. Additional studies to characterize the role of this tubular damage in CP-ARF are needed.

COMPENSATORY ADAPTATION TO UNINEPHRECTOMY (NX) IN THE NEWBORN: COMPARISON WITH NORMAL RENAL MATURATION. Robert L.Chevalier, University of Virginia, Department of Pediatrics, Charlottesville, VA.

The renal response to NX in the newborn guinea pig (NBGP) was compared with the pattern of normal development. Right NX or sham (S) operation was performed within the first 36 h of life. At 10±1 d and 22±1 d, under Inactin anesthesia, left kidney glomerular filtration rate (LKGFR) was measured, and superficial single nephron GFR (SNGFR) was determined by micropuncture. Number of glomeruli (NG) was counted at 1, 10, and 22 d using acid digests of India ink perfused kidneys.

Age (d)	Group	LKGFR (µl/min)	SNGFR (nl/min)	NG (x10^3)
1		-----	-----	70±2 (4)
10	S	271±42 (7)	2.8±0.5 (7)	70±2 (4)
	NX	395±59 (8)	4.9±0.5* (7)	79±8 (4)
22	S	539±44† (9)	7.2±0.5† (8)	68±2 (6)
	NX	971±49*†(10)	11.0±0.7*†(9)	84±3*§(6)

±SE. (number animals). *,p<0.05 vs S groups; †,p<0.05 vs 10 d in same group; §,p<0.05 vs 1 d.

At 10 d, SNGFR for NX animals was 77% greater than for the S group while LKGFR was not significantly greater (mean 46% increase). At 22 d however, LKGFR for the NX group exceeded that for S animals by 80%, with a rise in SNGFR of 52% and increase in NG by 20%. It is concluded that NX in the NBGP results in an acceleration of superficial nephron maturation, but differs from normal renal development by formation or recruitment of additional nephrons.

EFFECT OF RAISED PERFUSATE CALCIUM IN THE PRE- AND POST-ISCHEMIC ISOLATED KIDNEY. A.J. Cohen, R. Rossetti*, and J.C.S. Fray*. Depts of Med. and Physiol., Univ. of Mass. Med. School, Worcester, MA

To define the factors that control GFR and plasma flow before and after ischemia, a model in the isolated perfused rat kidney was employed. Kidneys were perfused with a recirculating Krebs-Henseleit medium consisting of 6.5 gm% albumin and either 2.5 mM (Lo Ca) or 7.5 mM (Hi Ca) perfusate calcium. Following 20 minutes of control perfusion (pre-I) kidneys were subjected to 30 minutes of complete ischemia by shutting off arterial flow and then reperfused for 20 minutes post-ischemia (post-I). Lo Ca kidneys had a pre-I urine flow (UF) of 41.4±8µl/min, a GFR of 0.61±0.08 ml/min, and F_ENa, 4.6±0.9%. Post-I, UF fell to 8.9±2 µl/min (p<.0025 vs pre-I), GFR fell to 0.05±0.02 ml/min (p<.0001 vs pre-I) and F_ENa rose to 13.4±2.2% (p<.01 vs pre-I). Perfusate flow (RPF) did not change after ischemia (pre-I= 20.8±0.9 ml/min/g vs post-I=21.4±1.4; p=NS). Hi Ca kidneys had similar reductions in UF and GFR following ischemia (pre-I UF=21.4±6 vs post-I UF= 5.4±2.2 µl/min; p<.025 and pre-I GFR 0.37±0.1 vs post-I 0.08±0.04 ml/min; p<.05. However, in contrast to Lo Ca, Hi Ca kidneys had a reduction in RPF, post-I, as previously reported (Cohen, Baker and Fray, Kidn Int 16: 772). Despite similar pre-I RPFs, pre-I UF and GFR were significantly lower (p<.05) in the Hi Ca than in the Lo Ca kidneys.

Thirty minutes of ischemia in the isolated kidney as in the intact animal, produces a reduction in GFR and UF and an increase in F_ENa following reperfusion. Reperfusion is unaccompanied by vasoconstriction unless Ca is sufficiently high. Raising perfusate Ca appears to reduce GFR and UF pre-I independent of changes in RPF.

● DECREASED VASCULAR SENSITIVITY IN THE IMPAIRED RENAL BLOOD FLOW (RBF) AUTOREGULATION OF ACUTE RENAL FAILURE (ARF). John D. Conger and John B. Robinette.* Univ. of Colorado Health Sciences Center, Denver, Colorado.

In a previous report (Proc. Amer. Soc. Nephrol 12:80A, 1980) a loss of RBF autoregulation was shown in norepinephrine (NE) and mercuric chloride ARF in rats. In this study renal vascular sensitivity to physiologic agents in ARF was tested by comparing dose-response curves to angiotensin II and acetylcholine in control (C) and 1 and 3 wk NE-infused rats. RBF (ml/min) responses were as follows:

	Angiotensin II(μg/Kg/min)			
	Saline	.0032	.0128	.0512
C (N5)	7.8±.3	7.8±.3	6.6±.4	3.8±3.3
NE-1 wk(N5)	7.9±.5	7.9±.5	9.0±.8	9.7±1.6
NE-3 wk(N6)	7.7±.5	7.6±.3	5.2±1.3	2.7±.3

There were significant declines in RBF with each increment of angiotensin II in C and NE-3 wk ($p<0.01$). The trend to increasing RBF in NE-1 wk correlated with progressive rise in systemic blood pressure. RBF(ml/min) response to acetylcholine was:

	Acetylcholine (μg/Kg/min)			
	Saline	.0032	.0128	.0256
C (N5)	8.5±.6	8.9±1.1	12.5±.9	13.8±.5
NE-1 wk(N5)	8.4±.4	8.4±.3	8.4±.2	8.4±.3
NE-3 wk(N6)	7.9±.3	8.2±.3	11.0±.7	13.0±1.1

Increases in RBF with each acetylcholine dose were significant ($p<0.01$) in C and NE-3 wk. There was no change in RBF in NE-1 wk. Glomerular filtrations were 30 and 85% of C in NE-1 and 3 wk, respectively.

It is concluded that vascular sensitivity is reduced at 1 wk in NE-induced ARF in rats.

CHANGES IN RENAL CORTEX ELECTROLYTE CONTENT AND Na-K-ATPase ACTIVITY IN EARLY GENTAMICIN (G) NEPHROTOXICITY. R. Cronin, K. Nix*, E. Ferguson*, and W. Henrich. VAMC and UTSW Med Sch, Dallas, Texas.

We have previously demonstrated that nephrotoxicity from a 10 day course of G in the dog is markedly enhanced with a low potassium (K) diet. The present study investigates the mechanism of this effect by examining 5 and 7 days of G (30 mg/kg/day) on plasma creatinine (PCr) and electrolyte content of renal cortex (RC) in K depleted (Lo K) vs K replete (Hi K) dogs (KCl 4 mEq/kg/day). Na-K-ATPase activity in RC was assessed on Day 7. Hypokalemia (4.5±.1 to 2.7±.2 mEq/L, $p<.001$) and systemic K depletion (skeletal muscle K 36.0±.5 to 27.3±1.7 mM/100g/FFDS, $p<.001$) developed only in Lo K dogs. After 5 days of G in Lo K and Hi K and after 7 days in Hi K dogs, PCr was unchanged from control. After 7 days of G in Lo K dogs, PCr rose from 1.2±.1 to 4.3±1.0 mg/dl, $p<.01$ and RC Na-K-ATPase activity was 20% lower than in Hi K dogs (5.9±.8 vs 8.0±.2 μM/ Pi/mg protein/hr, $p<.05$). RC Na, K, and P ($\bar{x}$ SEM) were:

		Sodium	Potassium	Phosphorus
		mM/100g/FFDS		
	C (16)	23.3±0.7	29.7±0.4	38.5±0.4
Day 5	Lo K (6)	22.7±0.6	24.8±0.4*	33.7±0.4*
	Hi K (6)	22.1±1.0	24.9±0.5*	34.8±0.5*
Day 7	Lo K (6)	27.9±1.7	22.7±0.6*	34.0±1.3*
	Hi K (6)	20.9±1.4	22.1±1.0*	33.0±1.2*

*$p<.05$ vs control (C); FFDS=fat free dry solids

Thus, 1) a Lo K diet and systemic K depletion accelerates G nephrotoxicity, and 2) depletion of RC K and P are consequences of G administration not preventable by a Hi K diet and suggest cellular injury that may predispose to G nephrotoxicity.

THE GENETICAL ASPECTS OF EXPERIMENTALLY INDUCED POLYCYSTIC KIDNEY DISEASE IN MICE. John F.S. Crocker and Stan R. Blecher*. Dalhousie Univ. and the Izaak Walton Killam Hospital for Children, Dept. of Pediatrics and Anatomy, Halifax, Nova Scotia.

Genetical factors play an important role in the etiology of some forms of polycystic kidney disease (PKD). However, virtually nothing is known of the molecular nature of the gene product defect(s), nor their site of action. A study of the genetically determined basis for susceptibility to steroid teratogens in the causation of PKD was begun. This model of PKD is induced by injecting a glucocorticoid acetate on the first day of life. The cysts occur, with renal failure, over the next week. In the present study only a percentage of animals within an experimental group showed susceptibility to the teratogen and there was no sex predilection. These studies, on random bred SWR (Swiss White) mice, as well as some inbred strains such as Eg° and DBA have provided preliminary confirmation of the prediction that randomly bred strains will demonstrate high variance and inbred strains low variance. Thus we have preliminary evidence of genetic control of susceptibility to inducible PKD.

Biddle and Fraser studying steroid induced cleft palate susceptibility to the teratogen showed it was influenced by a small number of genes. It is possible that a similar situation pertains to polycystic disease of the kidney.

SODIUM RETENTION IN EXPERIMENTAL NEPHROTIC SYNDROME (NS):TRADITIONAL THEORY vs. PRIMARY RENAL SODIUM RETENTION. G.M.Danovitch and R.Papendick*.Nephrology Division, UCLA School of Medicine, Los Angeles, CA.

In contrast to traditional teaching it has recently been suggested that the renal sodium retention of NS may not depend on extrarenal factors but may be related to intrinsic renal factors such as resistance to flow of protein containing tubular fluid. To evaluate this further we applied a systemic natriuretic stimulus to nephrotic rats while their protein excretion was increasing. Hyperoncotic albumin (0.6% BW) was infused into three groups of conscious rats. In 9 control rats sodium excretion ($U_{Na}V$) rose from 5.5 to 10.3 μEq/min as plasma volume (PV) rose by 14%. In 12 edematous rats with puromycin induced NS, PV rose by 23%, protein excretion doubled and $U_{Na}V$ rose from 0.6 to 14.0 μEq/min. To exclude the possibility that this enhanced natriuretic response to PV expansion in NS animals was related to their reduced GFR (1.2±.2 vs. 2.6±.2 ml/min) we studied a third group of 9 non-nephrotic rats with remnant kidneys (GFR 1.3±.1 ml/min). PV rose by 16% and $U_{Na}V$ rose from 2.7 to 9.0 μEq/min, an increase not significantly different from that in control rats. We conclude: 1)PV related natriuresis occurs in the face of an increase in tubular fluid protein content suggesting that this intrarenal factor does not determine sodium retention in NS; 2) the enhanced natriuresis following albumin infusion in NS is not related exclusively to decreased GFR but possibly to the greater degree of volume expansion following increased oncotic pressure in edematous animals; 3) the persistence of sodium retention in this model of NS is secondary to hypoproteinemia and decreased PV and is not due to a primary renal sodium retaining state.

HYDRONEPHROSIS INDUCES RENAL CORTICAL PROSTAGLANDIN SYNTHESIS: POSSIBLE MEDIATION BY CELLULAR INVASION. Bernard B. Davis and Philip Needleman. Washington Univ. and St. Louis Univ. and VA Medical Center, St. Louis, Missouri.

The hydronephrotic kidney (HNK) perfused ex vivo, demonstrates markedly enhanced prostaglandin (PG) thromboxane (TX) synthesis which is related to new protein synthesis. That phenomena was investigated using cortical (C) and medullary (M) slices from HNK and contralateral kidney (CK). Slices were incubated in Krebs media, gas phase 95% O_2, 5% CO_2. Incubation media were analyzed for PGE2 by RIA. C slices from CK had low basal levels (0.02 ± .01 ng/mg wet wt.) and did not respond to bradykinin (BK) (.02 ± .01). By contrast, C from HNK had higher basal .15 ± .03 levels and responded to BK .37 ± .06. PG production in HNK C increased with time of incubation, at 5 hrs BK was 1.29 ± .18 and basal .35 ± .04. Aspirin given in vivo completely inhibited the 1 hr values but there was recovery by 5 hrs, 0.65 ± .07. Cyclohexamide inhibited both the time dependent increase and recovery from aspirin. By contrast, BK increased PGE_2 in M from both HNK and CK. To ascertain if a proliferative cell was responsible for enhanced PG synthesis cyclophosphamide (CPA) 50 mg was administered at the time of ligation and 48 hrs later. CPA inhibited the time dependent increase in PG synthesis and uncovering of BK sensitivity. Administration of CPA 80 hrs post ligation had no effect. CPA had no effect on medullary PG production. These data indicate induction of new PG synthetic enzymes in HNK-C and that these responses are related to the invasion and proliferation of a new cell in cortical tissue. This response may also occur in other renal diseases.

AMINONUCLEOSIDE(An)-INDUCED CHRONIC GLOMERULOSCLEROSIS(GS), RENAL ARTERIOLAR THICKENING & NECROSIS IN SUCROSE-LARD-CASEIN(SLC)-FED HYPERTENSIVE RATS(SHR): ENHANCEMENT BY HYPERLIPIDEMIA & PROTECTION BY HYDRALAZINE &/OR HALOFENATE. K.David G. Edwards, Nancy W.Alcock* & Conrad L.Pirani, Cornell & Columbia Univs.& Memorial Hosp., New York, NY.

Hyperlipidemia, hypertension and a chemical nephrotoxin in combination may cause chronic renal disease. In this half-a-life-span study in SLC-fed female SHR, we have measured systolic BP(SBP,mmHg), plasma total cholesterol(PTC,mg/dl) & proteinuria (UPr,mg/mg creatinine) 1 y after 1 i.p.i. of An(90 mg/Kg.)+chronic hydralazine(Hdz,80mg/L.)+halofenate (Hal,0.05% of diet). Renal pathology was evaluated double-blind before breaking the code by semi-quantitation(+'s), with particular attention to focal, global & total GS & renal arteriolar thickening (Thg) or arteriolar necrosis (Nec)(see Table):-

Table:	Av. (n)	SBP	PTC	UPr	Glmlscl(GS) FGS+GGS=TGS			Arteriolar Thg	Nec
SLC/SHR	(5)	138	99	9	0.2	0.1	0.3	0.3	0
"/"+Hal	(8)	132	63'	9	0	0	0	0.1	0
"/"+Hdz	(6)	80'	84	7	0	0	0	0	0
"/"+"+Hal	(8)	81'	50'11		0	0	0	0	0
"/"+lAn	(8)	166	215'85'		1.7'	2.7'	4.4'	2.8'	1.1
"/"+"+Hal	(8)	134*	98*44*		1.2	0.8*	2.0*	0.9*	0*
"/"+"+Hdz	(7)	96*	117*31*		1.1	0.6*	1.7*	0.6*	0*
"/"+"+"+Hal	(8)	89*	82*38*		0.8*	0.6*	1.4*	0.4*	0*
SHLC(Cntrl)	(2)	150	74	6	0.5	0	0.5	0	0

*signif.diff.cf.SLC/SHR+lAn($P < 0.05$); 'sig.SLC/SHR

The most severe lesions including arteriolar Nec (malignant hypertension) were seen only in the untreated hypercholesterolemic, hypertensive SLC/SHR exposed to 1 i.p.i. of An. The severity of the renal lesions was markedly reduced by either Hal or hydralazine therapy and even more so by Hal+Hdz.

RENAL EXCRETION DISTRIBUTION AND METABOLISM OF ^{14}C ETHYLENEDIAMMINE DICHLOROPLATINUM (CDEP) IN RATS. M. Daye*, P. Miller*, J. Guttenplan*, M. Goldstein and R. Safirstein, Mt. Sinai Sch. of Medicine, N.Y.

Liganded platinum (Pt) compounds are antineoplastic and nephrotoxic. Previous studies demonstrate that the concentration of elemental Pt is highest in the kidney. Since there may be a relationship between the localization of Pt in the kidney and its toxicity, ^{14}C-labeled CDEP was given to rats to determine its renal clearance, distribution and metabolism.

Rats given 10mg/kg CDEP develop polyuric renal failure comparable to that induced by cis-dichlorodiammine Pt, the parent compound. Thin layer chromatography of plasma ultrafiltrates and urine reveal several chemical species different from purified CDEP, but ^{14}C-activity in urine was not diminished by $Ba(OH)_2$ precipitation or by organic solvents which extract ethylenediammine (en). Thus the en-Pt bond is intact. Kidney homogenates showed highest activity (DPM/mg protein) in the inner cortex-outer medulla with further enrichment in the cytosolic fraction. Tissue slice studies show a kidney slice/medium ratio of 3.6±.1 (4h at 60uM).

CDEP binds rapidly and extensively (95% at 24h) to plasma proteins and its plasma disappearance is characterized by a rapid early phase ($T_{½}$ 41 min) and a slower later phase ($T_{½}$ 2.6d). Of the total dose, 41% is excreted in one and 54% by 24 hrs. In constant infusion experiments, the clearance ratio of CDEP/inulin is 1.10±.03 ($p<.025$).

The results suggest that CDEP or its metabolites are secreted by and concentrated in the renal tubule cells. Inhibiting the uptake of CDEP may prove effective in decreasing its nephrotoxicity.

HYPOCHOLESTEROLEMIC EFFICACY OF A VASODILATOR DRUG, HYDRALAZINE, ALONE AND COMBINED WITH HALOFENATE: PROTECTION AGAINST AMINONUCLEOSIDE-INDUCED CHRONIC RENAL FAILURE IN SUCROSE-LARD-CASEIN(SLC)FED HYPERTENSIVE RATS(SHR). K.D.G.Edwards & Nancy W.Alcock*, Cornell/Memorial Sloan-Kettrng Cncr Ctr,New York,NY

Hyperlipidemia may be a host-kidney risk-factor when associated with physical injury(high BP) or chemical injury(aminonucleoside, An), or both, enhancing the induction & development of a progressive chronic renal failure. In this 1 y study in SLC-fed SHR, we measured plasma triglycerides(PTG) & cholesterol(PTC,mg/dl), systolic BP(SBP,mmHg), body weight as % of initial wt.(BW%), 2-kidney wt. (2KW,Gm.), proteinuria(UPr,mg/mg creatinine), BUN (mg/dl) & approx.GFR(% of normal=20/Pcreat)(Table):

Table:	Av.	PTG	PTC	SBP	BW%	2KW	UPr	BUN	GFR%
SLC/SHR	(5)	493	99	138	131	1.58	9	26	100
"/"+Hal	(8)	158'	63'	132	117'	1.48	9	20	70
"/"+Hdz	(6)	209'	84	80'	130	1.35	7	21	90
"/"+"+Hal	(8)	218'	50'	81'	118'	1.41	11	29	76
"/"+lAn	(8)	387	215'	166	119	2.59'	85'	97	26'
"/"+"+Hal	(8)	263*	98*	134*	117	1.81*	44*	28*	137*
"/"+"+Hdz	(7)	350	117*	96*	130	1.86*	31*	26*	86*
"/"+"+"+Hal	(8)	247*	82*	89*	119	1.67*	38*	35	88*
SHLC-Contr	(2)	149	78	150	126	1.49	6	21	100

*signif.diff.cf.SLC/SHR+lAn($P < 0.05$); 'sig.SLC/SHR

Analysis of variance of this 2^3 factorial study (Hdz,0 or 80mg/L.; Hal,0 or 0.05% of diet;& lAn, 0 or 90mg/Kg.in 1 i.p.i. being the 3 factors at two dose-levels) showed that Hdz & Hal significantly lowered elevated PTC levels, in the presence or absence of An-induced renal failure; the lowest PTC were seen with combined therapy. Renovascular damage induced by An(Edwards et al.,ASN Abstract,1980) significantly elevated PTC. Hdz & Hal lowered PTG in absence of An, but Hdz was ineffective vs.TG+An.

ACQUIRED GENTAMICIN (G) INSENSITIVITY: RATE OF FUNCTIONAL RECOVERY WITH CONTINUED DRUG ADMINISTRATION. W. Clayton Elliott, and William M. Bennett. Univ. of Oregon Hlth. Sci. Ctr., Div. of Nephrol., Portland, Oregon.

We have previously shown that rats with G mediated, acute renal failure recover, both histologically and functionally, despite continuous G administration. To better evaluate this acquired insensitivity to G, we administered G, 40 mg/Kg/day for 14 days, to male F344 rats. G was then either stopped (Group I) or continued for seven more days (Group II). On the 22nd day inulin clearance (CIn), in vitro para-aminohippurate (PAH) and N-methylnicotinamide (NMN) uptake was also determined by incubating renal cortical slices in Cross and Taggart media with PAH and NMN for 90 minutes at 25°C under O_2. Uptake was expressed as slice to media ratio (SM).

Group	CIn	PAH SM	NMN SM
No Rx	.87±.10 (6)	11.4± .8 (16)	5.5±.6 (16)
I	.60±.02 (4)[1]	6.2 ±1.4 (8)[1]	3.8±.7 (8)
II	.48±.19 (6)[1]	6.8 ±2.2 (7)[1]	3.1±.3 (7)

CIn expressed as cc/min/100 Gm body weight.
( ) = N in group.
[1]p<.05 compared to "No Rx" group. I vs II: p NS.
CIn at other treatment points: 3d=.79±.12 (4); 7d=.61±.18 (6); 10d=.18±.17 (5); 14d=.07±.06 (8).

We conclude that the rate of functional recovery from G mediated acute renal failure is not reduced by continued G administration. Our results suggest that a high degree of insensitivity to G toxicity develops in animals recovering from acute G injury.

EVIDENCE OF MICROPOLYPS IN CONGENITAL MODELS OF INFANTILE POLYCYSTIC DISEASE. Andrew Evan, Elizabeth Pearcy, & K.D. Gardner, Jr., Indiana Univ. Dept. of Anatomy and Univ. of New Mexico, Dept. of Medicine.

Our recent observations indicate that polypoid hyperplasia of the medullary collecting duct characterizes a variety of renal cystic disorders in man and rats. We have hypothesized that micropolyps participate in cyst formation by increasing resistance to the outflow of tubular urine. The present study examined two forms of heritable infantile polycystic kidney disease (IPKD) to establish the presence and distribution of polyps. Cystic kidneys from kittens and piglets were fixed with formalin and routinely prepared for light and scanning electron microscopy (SEM). Light microscopy revealed dilated collecting tubules with focal areas of epithelial hyperplasia and occasional micropolyps in both models. SEM clearly showed areas of polypoid hyperplasia. Micropolyps were seen along cystic collecting tubules where the polyp could cause partial obstruction or randomly situated on the cyst wall. The polyps varied in size and usually possessed a core. We conclude that polypoid hyperplasia is characteristic of IPKD as well as for induced and adult forms of human polycystic kidney disease. These data strengthens the possible role of micropolyps in the pathogenesis of polycystic kidney disease.

EVIDENCE FOR OPERATION OF THE MAGNIFICATION PHENOMENON IN PATIENTS WITH CHRONIC RENAL INSUFFICIENCY (CRF). Murray Epstein, David Hoffman*, & Arthur DeNunzio*, Dept. Medicine, Univ. of Miami School of Medicine & VA Medical Center, Miami, FL.

It has been proposed that the functional adaptations of surviving nephrons in advancing chronic renal failure are characterized by an excretory response which varies inversely with the number of surviving nephrons (Magnification Phenomenon). Because validation of this hypothesis in man is incomplete, we undertook to characterize the excretory response to acute volume expansion in patients with CRF. In normals, water immersion to the neck (NI) results in a redistribution of blood volume with preferential central hypervolemia (CV) in the absence of plasma compositional change. NI was utilized, therefore to assess the response to acute CV. Fourteen patients with CRF (GFR= 3 to 30 ml/min) were studied twice while ingesting a constant diet (60-120 meq Na/day): during a seated control study (C) and during 4-h of NI. FE_{Na} was constant during C. In contrast, during NI, there was a prompt and marked increase in FE_{Na} which markedly exceeded that of 29 normal subjects (Norm) undergoing an identical study.

FE_{Na}%	Prestudy	hr 1	hr 2	hr 3	Recovery
CRF	3.6±0.9*	5.7±1.1*	7.7±1.5*	8.4±1.5*	3.9±0.7*
Norm	0.5±0.0	0.7±0.1	1.1±0.1	1.3±0.1	0.9±0.1

Mean ± SE; *p < 0.05 vs. Norm

In the CRF group the extent of the augmentation of FE_{Na} during immersion varied inversely with GFR ($r= -0.53$; $p < 0.05$). These results provide evidence that the "magnification phenomenon" subtends renal sodium handling in patients with CRF.

● PROTECTIVE EFFECT OF (1-SAR,5-ILE,8-GLY) ANGIOTENSIN II (AI) IN THE RENAL FAILURE OF THE GENERALIZED SHWARTZMAN REACTION (GSR). Sandor A. Falk,* John D. Conger, Stephen Guggenheim. Univ. of Colorado Health Sciences Center, Denver, Colorado.

In a previous report (Proc. Amer. Soc. Nephrol. 11:89A, 1978) it was shown that the early acute renal failure of the GSR was due to afferent and lesser efferent arteriolar constriction. Despite systemic consumption coagulopathy, glomerular fibrin deposition was not in proportion to the magnitude of renal failure. The present study was designed to functionally inhibit afferent and efferent vasoconstriction in GSR without interfering with systemic consumption coagulopathy. In Gr. I was 8 Munich-Wister rats infused with E. coli endotoxin (E) at 0.65 mg/hr. Gr. II (N-6) was infused with E at the same dose but was also given AI at 2 µg/Kg/min prior to and during E. Hematocrits, blood pressures, and platelet counts were not different in Gr. I-II prior to E. Glomerular filtration rates (GFR) prior to E were 713±184 and 668±119 µl/min. respectively, in GR I-II (p=NS). After 2 hr E GFR was 35±42 and 411±226 µl/min. respectively, in Gr. I-II. The decline in GFR was significantly less in Gr. II ($p<0.01$). Glomerular fibrin deposition and declines in platelet counts were similar in Gr. I-II.

It is concluded that a functional vasopressor mechanism mediated by the renin-angiotensin system is in large part responsible for early renal failure in GSR.

● EVIDENCE OF PROXIMAL TUBULAR (PCT) "MEMORY" IN EXPERIMENTAL RENAL DISEASE. Leon G. Fine, Walter Trizna*, Yaacov Bar-Khayim*, and Norimoto Yanagawa*. Division of Nephrology, Center for the Health Sciences, UCLA School of Medicine, Los Angeles, CA.

In experimental models of chronic renal disease, an increase or decrease in single nephron filtration rate (SNGFR) is associated with parallel changes in proximal tubular fluid reabsorption (Jv). In order to assess whether intrinsic changes in tubular function contribute to these adaptations, Jv and transepithelial potential difference (PD) were studied in superficial PCTs obtained from normal rabbit kidneys (N), kidneys with increased SNGFR (remnant and uninephrectomy), and kidneys with decreased SNGFR (microsphere-embolized). Tubule size was measured as protein/mm and cellular volume/mm. Tubules were perfused at high and low perfusion rates to simulate in vivo conditions.

	SNGFR	Azotemia	Jv (nl/mm/min)	PD (mV)	Tubule Size
Normal	N	-	1.00±0.09	-3.6±0.2	N
Remnant	↑	+	1.66±0.16	-6.6±0.8	↑
Uni-Nx	↑	-	1.38±0.08	-6.8±0.8	↑
Embolized	↓	-	0.62±0.07	-1.7±0.3	N

Conclusions: 1. In experimental renal disease, "memory" of in vivo fluid reabsorptive pattern of the PCT is retained and expressed in vitro. 2. Jv and PD are increased in disease models having an increase in SNGFR and decreased when SNGFR is decreased. 3. Neither tubule size nor chronic azotemia can account for these intrinsic adaptations of PCT function which appear to be induced by long-term changes in nephron filtration rates.

● **NEPHROTOXICITY OF MYOGLOBIN IN THE RAT: RELATIVE IMPORTANCE OF URINE pH AND PRIOR DEHYDRATION.** **Guillermo Garcia,* Thomas Snider,* Michael Feldman* and David H. Clyne. V. A. Med. Ctr. and Univ. of Cincinnati Med. Ctr., Cincinnati, Ohio.**

Both prior dehydration and aciduria have been implicated in the genesis of myoglobinuric acute renal failure. To investigate the importance of each factor, both dehydrated (D) and non-dehydrated (N) rats were infused with equine myoglobin (1mg/min) under conditions of NaCl, Na_2SO_4 and $NaHCO_3$ diuresis. After 70 min. equilibration, rats were studied for two 30 min. control periods (C) and then 4 protein infusion periods (E). Non-myoglobin infused rats served as controls. Inulin clearances μ l/min/100G (mean ±SE) were as follows:

	NaCl(N)	NaCl(D)	Na_2SO_4(N)	Na_2SO_4(D)	$NaHCO_3$(N)
C	110±6	101±4	94±4	70±3	109±4
E	75±4†	30±4†	52±3†	40±2†	80±2†

† p <0.0005 (C v's E and E myoglobin v's E control)

GFR fell rapidly in the first E period with infusion of small amounts of myoglobin. Acute, non-oliguric renal failure developed in group NaCl(D) but in other groups GFR stabilized at a lower level with increased FENa. Immunohistology showed cast precipitates of myoglobin and Tamm Horsfall glycoprotein in medullary collecting ducts. This was maximal in the NaCl(D) group, moderate in the Na_2SO_4 groups, mild in the NaCl(N) group and absent in the $NaHCO_3$ group. It is concluded that infusion of myoglobin produces an early, consistent fall in GFR under a variety of conditions. This is greatly magnified by prior dehydration. Cast formation is dependent on urine pH, is not a factor in the initial fall in GFR but may be important in the establishment of acute renal failure.

● CYTOSKELETAL DEFECT IN CORTICAL COLLECTING DUCT CELLS IN LITHIUM-INDUCED POLYURIA. J.N.Forrest, Jr., T.W.Marcy, D.Biemesderfer and M. Kashgarian, (Intro. by H.V.Murdaugh) Yale Univer.Sco.Med., New Haven, CT.

Lithium polyuria has been associated with renal morphologic changes in man and rat. To determine the chronic effects of Li on morphology, Sprague-Dawley rats receiving Li^+(4 mEq/kg BW/d in food) for 8 wks were compared to controls (C) and rats with comparable polyuria induced by drinking glucose water (P). Compared to C, Li^+rats (P_{Li} 0.92 mEq/L) had identical GFR, increased urine flow (2.6±0.6 ml/h 100 g BW vs 0.2±0.01) and decreased U_{Osm} (230±40 mOsm/kg vs 1280±290). In contrast to P rats, Li^+rats could not increase U_{Osm} after DDAVP (320±90 vs 1475±140). Following perfusion fixation renal morphology was scored blindly. By light microscopy only modest interstitial changes were seen with similar scores (0-4 scale) in Li and C rats (1.2±0.4 vs 0.7±0.2); however, P rats had greater changes compared to C (2.1±0.4, $p<0.01$). On electron microscopy, a striking lesion was associated with Li. In 8 of 8 Li^+ rats but in no C or P rats distinct cytoplasmic aggregates of intermediate microfilaments were observed in cortical collecting duct (CCD) cells. Microfilament bundles were prominent in perinuclear regions of principal cells but were not seen in intercalated cells or in proximal or distal tubular cells. Microfilament bundles were seen as early as 2 wks on Li. We conclude that in the rat (1) intestinal inflammation is not prominent in Li polyuria but is seen in glucose-polyuric controls (2) Li polyuria is associated with a unique defect in the cytoskeletal system of CCD cells. These findings suggest that Li polyuria may result, in part, from disruption of cellular function dependent on microfilaments.

● DIMINISHED TUBULAR BACKLEAK BY THE POST-ISCHEMIC INFUSION OF ATP-$MgCl_2$. Karen M. Gaudio,* Norman J. Siegel, Irshad Chaudry,* and Michael Kashgarian. Yale Univ. Sch. of Medicine, New Haven, CT.

The infusion of ATP-$MgCl_2$ will enhance recovery from an ischemic renal insult. To study the effect of this agent on individual nephrons, rats were subjected to 45 minutes of renal ischemia and then treated with either ATP-$MgCl_2$ (25 μmoles) or 0.9% saline (NS). One day later, whole kidney inulin clearance was significantly greater in ATP-$MgCl_2$ treated animals (544 ± 49 μl/min/100 gmBW, $P < 0.01$) than in NS infused rats (286 ± 28), although both groups were less than control values (1109 ± 51). In contrast, superficial single nephron C_{in} (SNC_{in}) attained control values in ATP-$MgCl_2$ rats (38.6 ± 5.9 nl/min) and was mildly reduced (22.6 ± 2.1) in NS animals.

To evaluate the discrepancy between whole kidney and SNC_{in}, the effect of ATP-$MgCl_2$ on tubular backleak was studied. Following the microinjection of H^3-inulin into early proximal tubules, inulin recovery was significantly less in NS treated rats (72 ± 7%, $P < 0.01$) than in ATP-$MgCl_2$ treated rats (92 ± 3%) or control animals (98 ± 2%). To define the site of tubular backleak, SNC_{in} was measured from a proximal and distal convolution within the same nephron. In NS treated animals, there was a significant decrease in SNC_{in} (8.5 ± 3.4 nl/min, $P < 0.01$) between these sites whereas no significant change in SNC_{in} occurred in either the ATP-$MgCl_2$ rats (2.3 ± 2.7) or control animals (0.9 ± 2.2).

These data indicate that the salutory effects of ATP-$MgCl_2$ are achieved, in part, by diminishing the degree of tubular backleak which occurs in an ischemic renal insult.

THE EFFECT OF FUROSEMIDE (F) ON CIS-DIAMMINEDICHLOROPLATINUM (CP) INDUCED ACUTE RENAL FAILURE (ARF). M. Gehr, S. Chopra, J. Kaufman, D. Chase*, and W. Flamenbaum. Renal Sections, Boston VA Medical Center and Lemuel Shattuck Hospital, Boston, MA.

CP (5mg/kg) can predictably induce ARF in 60% of male Sprague-Dawley rats at 96 hours. The efficacy of F to ameliorate the decrease in glomerular filtration rate and rise in creatinine (Cr) is controversial. We have studied the effect of F (12.5 mg/kg) i.p. given 30 minutes prior to the CP injection. Cage studies reveal significantly higher urine flow rates in CP and CP-F groups (15.8 ml/min and 14.6 ml/min) as compared to control (9.55 ml/min), and a significantly higher creatinine. Micropuncture data (urine to plasma inulin concentration ratios (U/P-In) and single nephron (SN) glomerular filtration rates (GFR) are shown below:

	GFR ml/min	U/P-In	SNGFR nl/min	Cr mg/dl
CONTROL	1.55	278.6	36.84	0.38
CP	0.50*	110.3*	27.03*	1.19*
CP-F	0.51*	101.3*	25.74*	0.84*

(*Significantly different from Control, $p<0.05$)

In this model urine flow was increased indicating a non-oliguric form of ARF. Cr rose, SNGFR and GFR fell significantly in both CP and CP-F treated groups as compared to controls. Tubular function was impaired as evidenced by the significant fall in U/P-In in both CP and CP-F groups. However, there were no significant differences in any of these parameters between CP and CP-F treated groups. Thus F has no protective effect in this CP ARF model.

RENAL CONCENTRATION DEFECT (RCD) FOLLOWING NON-OLIGURIC ACUTE RENAL FAILURE (ARF). J.A. Gordon, J. Kim, L. Peterson, M. Ellis, P.A. Gross, R.J. Anderson*, Dept. Med., Univ. Colo. Health Sciences Center, Denver, CO.

Nonoliguric ARF is associated with an RCD. We determined that 50 minutes of unilateral renal artery occlusion with contralateral nephrectomy results in nonoliguric ARF in the rat. In experimental animals (E, n=30), serum creatinine peaked at 5 mg/dl on day 3 and returned to control (C, paired fed/watered rats with unilateral nephrectomy alone, n=30) on day 7. On day 8, 30 hr. dehydration Uosm was lower in E (E, 1,725, C, 2,300 mOsm/kg, $p<.001$). Comparable ADH levels and impaired response to exogenous ADH in E documented a nephrogenic origin for this RCD. To evaluate a potential role for prostaglandins (PG), either PG inhibitors or placebo were administered to E animals (n=18) during 30 hr. dehydration. PG inhibition did not improve Uosm. To determine if diminished interstitial solute could be responsible for the RCD, medullary-papillary solute was measured following 30 hr. dehydration and significantly lower values were found (E, 900 vs. C, 1,500 mOsm/kg, n=19, $p<.001$). To determine if this diminished solute was due to vascular mechanisms, papillary plasma flow was measured and found to be equivalent in C and E. To examine a role for biochemical factors, renal medullary adenylate cyclase response to ADH was examined and found to be reduced in E kidneys (n=14, $p<.001$). These studies suggest a defect in generation of renal interstitial solute as one mechanism of the RCD. In vitro studies also suggest a potential role for impaired renal adenylate cyclase response to ADH in this disorder.

CHRONIC TUBULO-INTERSTITIAL(TI) DISEASE AFTER REPEATED DOSES OF CIS PLATINUM(PT). M.H.Goldstein, R.Safirstein & J.Churg, Mt. Sinai School of Medicine, New York, New York.

Chronic TI disease causes renal insufficiency in man, but its evolution and progression have been difficult to study experimentally due to lack of a suitable animal model. Since one dose of Pt induces reversible renal failure in rats, repeated doses of Pt were given in an attempt to produce chronic TI. 15 Sprague-Dawley rats received Pt(5mg/Kg B.W.i.p.) followed by one or more doses of 2.5mg/Kg B.W. at 3 to 4 week intervals. 4 to 7 weeks after the last dose of Pt, clearance, micropuncture and balance studies were performed. In 11 of 15 rats, renal insufficiency developed after 2 doses of Pt(mean BUN 49.7, range 22 to 152mg%). Following H_2O deprivation and ADH, Uosm was 733 and 3205 mOsm/Kg H_2O($p<.001$) while V was 13.9 & 1.5 ul/min($p<.001$) in Pt and control rats, respectively. In balance studies(n=3), $U_{Na}V$ fell with decreasing dietary Na intake from 3.2 to 0.4 mEq/d. C_{in} and C_{PAH} were 0.52 and 1.2ml/min respectively(n=5). The kidney surface was granular with occasional cyst formation and microscopically showed areas of dilated and collapsed tubules. SNGFR varied markedly, ranging from 3-129 nl/min. Light microscopy showed atrophic and dilated tubules with interstitial fibrosis and mononuclear cell infiltration, most prominent in the inner cortex-outer medulla; glomeruli were well preserved. The histologic changes correlated well with the severity of the renal failure. Thus, the functional and histologic findings are characteristic of chronic TI.

Repeated doses of Pt produce persistent renal insufficiency in rats, providing a promising experimental model for the study of TI disorders.

NUTRITIONAL STATUS OF NONDIALYZED PATIENTS WITH CHRONIC RENAL FAILURE. G. Grodstein, C. Roberts,* R. Winer, G. Shah, W. Davidson, S. Franklin, and J.D. Kopple, VA Wadsworth Medical Center, Harbor General Hospital, Long Beach VA Medical Center, University of California, Los Angeles and Irvine, Los Angeles, California.

There is increasing awareness of the problems of malnutrition and wasting in dialysis patients, even in otherwise healthy patients who are just starting dialysis. Since it is not known when wasting begins, we evaluated nutritional status in 25 men (M) and 10 women (F) with advanced but stable chronic renal failure (CRF). Mean age and creatinine clearance were 54±14 SD years and 9.9± 3.3 ml/min. Data were compared to 49 normal M and to standard tables for F. Anthropometry revealed decreased triceps and subscapular skinfold thickness and % body fat in M ($p<.01$) but not in F. Mid-arm muscle circumference was normal in both M and F, although creatinine-height index, a measure of muscle mass was low in both groups ($p<.01$). In both M and F serum albumin, transferrin, and C_3 were decreased ($p<.01$). Neither the cause of renal disease, GFR, age, marital status, employment, education, nor the scores on standard psychological tests correlated with nutritional status. Protein intake averaged 63 g/day near the normal RDA, but energy intake was only 25 kcal/kg/day. In general, nutritional parameters were less abnormal than in a group of patients undergoing their first dialysis. These findings suggest that wasting is present in stable CRF but is not as pronounced as in patients in whom dialysis is being initiated. Low energy intakes may contribute to the wasting. Careful nutritional monitoring and therapy may prevent progression of wasting in uremia.

EFFECTS OF INDOMETHACIN (INDO) ON THE DISEASED DOG KIDNEY BEFORE AND AFTER REMOVING THE CONTROL KIDNEY. Frank D. Gutmann. Univ. of Wisconsin, Mount Sinai Med. Ctr, Dept. of Med, Milwaukee, WI.

I investigated whether the enhanced natriuretic response to acute volume expansion in the unilateral pyelonephritic dog kidney (DK) before removing (Stage II) the contralateral control kidney (CK), or the compensatory increase in GFR in DK after removing (Stage III) CK, are prostaglandin mediated. Seven conscious, split-bladder dogs were studied before, 45 min after I.V. vehicle (V) or Indo (2 mg/Kg in 0.5% Na_2CO_3), and 5 minutes after rapid I.V. expansion with Ringer's lactate (75 ml/Kg). Using the foregoing 3-phase sequence, each dog was studied on 4 different days: V only or Indo in Stage II, and V only or Indo in Stage III. Creatinine for measurement of exogenous creatinine clearance was infused in 5% mannitol at 0.25 ml/Kg/min.

Baseline endogenous plasma creatinine averaged 1.1 mg/dl in Stage II and 2.7 in Stage III. Fractional excretion of sodium (FE_{Na}) before ($\bar{a}$) and after ($\bar{p}$) V or Indo and $\bar{p}$ volume expansion (VE) are depicted (*=p<.025, Wilcoxan):

	Stage	Vehicle (V)			Indo			Net Δ(Indo-V)	
		$\bar{a}$	$\bar{p}$	VE	$\bar{a}$	$\bar{p}$	VE	$(\bar{p}-\bar{a})$	(VE-$\bar{p}$)
CK	II	.68	.52	3.56	.72	.29	3.03	-.26*	-0.30
DK	II	.70	.70	5.28	.83	.39	3.97	-.44*	-1.00
DK	III	3.19	3.29	9.45	3.36	2.54	8.81	-.92*	-0.12

The GFR was not altered in response to Indo in either CK or DK in Stage II or Stage III. These results suggest that in this conscious dog model, Indo (1) did not alter GFR, (2) slightly reduced FE_{Na} prior to VE, but (3) assuming the dose of Indo was adequate and the effect sufficiently prolonged, did not alter natriuretic response to VE.

● STUDY OF ISOLATED NEPHRON SEGMENTS IN A RABBIT MODEL OF OBSTRUCTIVE NEPHROPATHY. M. J. Hanley and K. Davidson*. Univ. of Tx. Hlth. Sci. Ctr., Dept. of Med., San Antonio, Tx.

Considerable controversy exists on the effect of urine outflow obstruction on the intrinsic transport properties of various nephron segments. To examine these properties directly a rabbit model of unilateral ureteral obstruction for 24 hours was utilized and nephron segments were studied by the method of isolated tubule microperfusion. In clearance studies of the model, split renal function determinations demonstrated a reduced GFR, a high fractional Na excretion (FE_{Na}) and isosthenuria on the obstructed side. Tubular function was then assessed in the cortical collecting tubule (CCT) and the cortical thick ascending limb of Henle's loop (T-ALH) in segments obtained from obstructed and unobstructed kidneys. CCT function was assessed by measuring fluid movement (Jv) in response to increasing the bath osmolality 100 mOsm/Kg with raffinose and providing a maximum ADH stimulus (250 μU/ml). Jv in the CCT from the obstructed kidneys was reduced 75% (0.89±0.10 nl/mm/min vs. 0.22±.04 p<.001 (N=6)). Similar CCT studies performed using 8-chlorophenylthiocyclic AMP instead of ADH failed to correct the defect (0.92±0.13 nl/mm/min vs. 0.36±0.12 p<.02 (N=6)). T-ALH function was assessed by measurement of the ability to lower the chloride concentration (ΔCl) at comparable flow rates. ΔCl in T-ALH from the obstructed kidneys was 24% of control values (37±3 meq/L vs. 9±1 p<.001 (N=6)). These findings suggest that in this model 1) post obstructive isosthenuria may be due to a collecting tubule unresponsiveness to ADH and disordered ascending limb function, 2) ADH resistance occurs at a site beyond the generation of intracellular C-AMP, and 3) the high fractional FE_{Na} is due, in part, to impaired ascending limb function.

FAILURE OF ISOTONIC SALINE DRINKING TO PROTECT RATS FROM URANYL NITRATE (UN)-INDUCED ACUTE RENAL FAILURE (ARF). D. Haley, Dept. Anat. U.T. Hlth. Sci. Ctr., San Antonio, Tex. Intro. by R.E.Bulger

Chronic oral intake of isotonic saline has been reported to offer some protection against the rise in BUN and creatinine concentrations and decrease in creatinine clearance associated with experimentally-induced ARF. To better examine this protective effect, the course of ARF was assessed by functional and morphologic studies in two groups of rats. Group I drank tap water, and Group II received isotonic saline for 3 weeks prior to induction of ARF by the subcutaneous injection of UN (10mg/kg). Only mild, transitory protection of renal function of Group II rats occurred.

	Inulin Clearance (ml/min/100g)		
5 h	0.68 ± 0.10	1.07 ± 0.11	p < .05
24 h	0.71 ± 0.08	0.94 ± 0.10	p < .05
48 h	0.43 ± 0.04	0.50 ± 0.08	n.s.
120 h	0.03 ± 0.01	0.12 ± 0.06	n.s.

There were no morphologic differences between the 2 groups as assessed with LM, SEM and TEM. Increased vesiculation and focal brush border loss were noted throughout the proximal tubule at 1 hour after UN. Focal areas of necrosis were apparent in the pars recta at 12 hrs. Thereafter there was progressive necrosis involving the majority of the proximal tubule by 120 hrs. Other morphologic changes occurred throughout the nephron, including the renal corpuscle.

These results indicate that, contrary to previous reports, oral intake of saline has little, protective influence on the course of UN-induced ARF in rats. The early functional differences noted may be attributed to the higher solute excretion rate attained by Group II rats on saline.

● EFFECT OF PRIOR FUROSEMIDE (F) INFUSION ON A RABBIT MODEL OF ISCHEMIC ACUTE RENAL FAILURE (IARF). M.J. Hanley and K. Davidson,* (intr. by S. Rosenblatt). U. of TX Hlth. Sci. Ctr., San Antonio, TX.

Rabbits subjected to 60 minutes of renal artery clamping develop an abrupt reversible rise in serum creatinine (10 mg/dl). Examination of tubule segments from this model has shown that proximal convoluted tubule (PCT) and proximal straight tubule (PST) reabsorption (Jv) is virtually eliminated coincident with the formation of tubular debris. It has likewise been shown that prior mannitol (M) infusion prevents the development of IARF and the associated tubular transport defects in this model. In the present studies rabbits were infused with F (20 μg/min/Kg) for 60 minutes prior to clamping. This prior infusion offered partial protection against the development of IARF (creatinine = 4 mg/dl). Function was then assessed in isolated tubules obtained from F treated control animals and from F treated animals subsequently subjected to 60 minutes of renal artery clamping. PCT and PST fluid reabsorption (Jv) of F treated ischemic tubules was reduced but not to the extent noted in these segments without F pretreatment. Thick ascending limb (T-ALH) ability to lower chloride concentration (ΔCl) of control and ischemic tubules was not significantly different. CCT Jv response to an ADH stimulus (250 μU/ml) of control and ischemic tubules was significantly different. The following values are given as % of control:

	PCT(Jv)	PST(Jv)	T-ALH(ΔCl)	CCT(ADH)
IARF	23%	12%	40%	38%
F	60%	69%	100%	49%
M	100%	100%	100%	69%

It is concluded that in this model a prior F infusion partially protects against the development of acute renal failure and the degree of protection correlates with the degree of preservation of proximal nephron function by F.

GLOMERULAR DYNAMICS IN RATS WITH MYOCARDIAL INFARCTS. T.H. Hostetter*, J.M. Pfeffer*, M.A. Pfeffer*, E. Braunwald*, and B.M. Brenner. Harvard Med. School, Brigham & Women's Hospital, Boston, MA.

The heart failure syndrome is marked by renal vasoconstriction despite ECFV expansion. To examine the microcirculatory basis of this phenomenon, we measured mean systemic ($\overline{AP}$) and glomerular transcapillary hydraulic pressures ($\overline{\Delta P}$), initial glomerular plasma flows (Q_A), and afferent (R_A) and efferent (R_E) arteriolar resistances during hydropenia and acute volume expansion (VE) with Tyrode's solution (4% bw) in Munich-Wistar rats 3 weeks after ligation of the left coronary artery. Animals were divided into two groups on the basis of histologically quantitated infarct size. C animals had infarcts involving 0-10% of the ventricular wall and MI rats had infarcts of 30%. LVEDP averaged 3.4±.8 vs. 17.6±5.0 mmHg (mean±SE, $p<.05$) in C and MI, respectively. Results ($^{\dagger}p<.05$ vs. hydropenia) include:

	$\overline{AP}$	$\overline{\Delta P}$	SNGFR	Q_A	R_A	R_E
	---mmHg---		---nl/min--		10^{10}dyn·s·cm^{-5}	
C(n=6)	116±3	39±1	41±6	117±14	3.5±.4	2.3±.3
MI(n=6)	112±3	38±2	46±4	106±17	3.4±.4	2.6±.3
C + VE	122±5	38±1	66±5†	189±23†	2.5±.3†	1.4±.3†
MI + VE	117±4	36±2	49±5	124±13	3.0±.3	2.6±.4

Thus, in hydropenia, SNGFR and its determinants did not differ between C and MI rats. During VE, however, SNGFR and Q_A failed to increase in MI rats due to persistant arteriolar vasoconstriction. This failure of renal vasodilation in response to VE in rats with large infarcts is presumably mediated by local and/or circulatory vasoconstrictor substances. Regardless of cause, the findings document a major renal hemodynamic defect in this clinically relevant model of heart failure in the rat.

EFFECTS OF ADRENALECTOMY (ADX) ON VASOPRESSIN (VP)-SENSITIVE cAMP METABOLISM IN MICRODISSECTED MEDULLARY NEPHRON SEGMENTS. B.A. Jackson,* R.M. Edwards,* and T.P. Dousa: (intr. by P.P. Frohnert). Mayo Clinic & Foundation, Rochester, MN.

Adrenal insufficiency is associated with an impaired urinary diluting ability in both man and experimental animals, but the precise loci along the nephron of this impairment remain unclear. We have examined VP-sensitive cAMP metabolism in two medullary nephron segments known to be intimately involved in urinary dilution and concentration, namely the thick ascending limb of Henle's loop (MAL), and collecting tubule (MCT) microdissected from 8-day ADX rats and sham-operated controls. VP-sensitive adenylate cyclase (AdC) in MCT of ADX rats did not differ from control values. However, VP-sensitive AdC was significantly lower in MAL of ADX rats compared to controls.

	MAL		MCT	
	Basal	10^{-6} AVP	Basal	10^{-6}AVP
Cont.:	15.1 ± 1.1	310.6 ± 35.8	27.1 ± 6.9	256.1 ± 13.8
ADX:	10.2 ± 1.8	203.2† ± 24.6	25.8 ± 7.3	245.7 ± 26.5

Mean ± SEM (fmol cAMP/30 min/mm length) † $P<0.05$ compared to corresponding control value.

cAMP-phosphodiesterase activity (10^{-6}M cAMP substrate) did not differ between controls and ADX in either MAL or MCT. Since recent microperfusion studies have suggested that VP and cAMP may stimulate NaCl transport in the thick ascending limb, the present data would suggest that the impaired urinary diluting ability seen in ADX may at least in part be due to a decreased generation of cAMP in the MAL in response to VP.

ROLE OF THE LUMINAL MEMBRANE IN THE ALTERED SOLUTE TRANSPORT WHICH OCCURS WHEN RENAL MASS IS DECREASED (Nx). Keith A. Hruska, Marc R. Hammerman,* and S. Klahr. Renal Division, The Jewish Hospital, Washington University, St. Louis, Missouri.

The tubular transport of many solutes is altered when renal mass is decreased. The location in the cell (luminal vs contraluminal membrane) where these alterations in solute transport occur has not been determined. To examine the effects of Nx on solute transport across the luminal membrane, brush border membrane vesicles (BBMV) were prepared from the viable portion of the kidney of Nx dogs and normal dogs. Initial transport rates of glucose, amino acids (proline), or phosphate (Pi), determined in the presence of a Na^+ gradient (Na out > Na in), were decreased in BBMV from Nx dogs as compared to controls. However, initial rates of ^{22}Na uptake in BBMV from Nx dogs were increased suggesting a more rapid dissipation of the Na^+ gradient in these vesicles, possibly due to increased Na^+ permeability. Therefore, initial rates of transport were measured under Na^+ equilibrated conditions (no Na^+ gradient). Under these conditions, no differences were found in the transport rates of glucose or proline between BBMV from normal or Nx dogs. However, Pi uptake was still decreased in BBMV from Nx dogs (12.9 ± 2 vs 24.1 ± 2 pmoles/ng protein in controls). Parathyroidectomy of Nx dogs prior to preparation of BBMV abolished this decrease in Pi uptake. We conclude that the alterations in solute excretion associated with decreased renal mass are accompanied by changes in Na-coupled transport across the luminal membrane of the renal tubule. In the case of Pi, a specific effect of parathyroid hormone on the luminal membrane contributes to decreased Pi uptake.

FAILURE OF VERAPAMIL TO REVERSE MYOHEMOGLOBINURIC ACUTE RENAL FAILURE IN AWAKE RATS. Bruce Jackson, Kenneth Kornetsky and Donald E. Oken, Departments of Medicine, Veterans Administration Hospital and Medical College of Virginia, Richmond, Virginia.

Various studies support and others argue against a key role of the renin-angiotensin system in experimental acute renal failure. Verapamil, an inhibitor of intracellular calcium transport, infused I.V. at 20 µg/Kg BW min. reportedly reverses the constrictor and Kf effects of pharmacologic doses of angiotension II (A2) on the renal microcirculation of normal rats. To determine whether A2 is essential to the pathogenesis of myohemoglobinuric acute renal failure (ARF), awake rats were infused continuously with verapamil 30 µg/Kg BW min in 0.0375 ml saline or saline 24h after glycerol injection. In normal control rats, glomerular filtration rate (GFR) measured by inulin clearance (C_{IN}) was 2.68±SEM 0.35 ml/min and mean B.P. 113.8±1.2 mmHg; after 2h continuous verapamil, B.P. fell to 99.4±3.8 mmHg ($p<0.05$) and GFR was unchanged ($p>0.1$). 24h after onset of ARF, C_{IN} of untreated rats was 0.03±0.01 ml/min and did not change after simple volume expansion alone ($p>0.5$) or after expansion and intravenous infusion of 30 µg/Kg BW min verapamil: C_{IN} 0.02±SEM 0.01 ml/min at 1-2h, 0.03±0.01 at 2-3h, 0.04±0.02 at 3-4½h. B.P. did not fall significantly with verapamil in the ARF rats ($p>0.5$). Thus, large amounts of verapamil given to awake rats with established myohemoglobinuric ARF are incapable of reversing filtration failure. The results argue against an essential role of angiotensin in the pathogenesis of this form of experimental ARF.

REDUCTION OF RENAL AND CARDIAC $Na^+ + K^+$ ATPase ACTIVITY IN CHRONICALLY DIGITALIZED DOGS. Robert E. Jackson,* Susan L. Neldon,* and Bohdan R. Nechay. Univ. of Texas Med. Branch, Dept. of Pharmacol. & Toxicol., Galveston, Texas.

Large doses of cardiac glycosides inhibit renal $Na^+ + K^+$ ATPase in acute experiments. After a certain threshold is reached natriuresis results. It is not known whether inhibition of cardiac $Na^+ + K^+$ ATPase mediates positive inotropism or is only a manifestation of cardiotoxicity. We studied the kidney function and enzyme activity in 5 healthy male dogs who received a therapeutic regimen of digoxin ($\sim$0.025 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) p.o. for 2 to 4 months. This resulted in plasma digoxin concentrations of 1 to 4 ng/ml. EKG's monitored throughout the project showed no changes. Six male dogs received gelatin capsules and served as controls. No change in plasma electrolytes, urinary dilution and concentration capacity (during water diuresis and hydropenia respectively), and Na^+ and K^+ excretion after a salt load (1 g/20 kg i.v.) was observed in either group of unanesthetized animals. GFR (exogenous creatinine clearance) per 1 m^2 was 11 to 24% higher in digitalized dogs than in controls. The animals were sacrificed with pentobarbital overdose for *in vitro* studies. In digitalized dogs, microsomal $Na^+ + K^+$ ATPase specific activity was 26 to 30% lower in renal cortex, medulla, and papilla, and 50% lower in left ventricle of the heart than in control dogs. Digitalization did not alter the osmolalities of renal tissues. We conclude that a 30% chronic inhibition of $Na^+ + K^+$ ATPase activity does not cause abnormalities in renal handling of electrolytes and water, and 50% inhibition of $Na^+ + K^+$ ATPase activity in the left ventricle causes no obvious EKG changes in the dog.

RESIDUAL RENAL FUNCTION IN NON-OLIGURIC ACUTE RENAL FAILURE. Rex L. Jamison and Bryan D. Myers, introduced by Norman S. Coplon. Stanford University, Division of Nephrology, Stanford, California.

We evaluated glomerular filtration (GF) and tubular reabsorbtive (TR) and secretory (TS) ability in 30 patients with acute azotemia following cardiac surgery. Fractional clearances of test solutes (Θ) relative to inulin clearance (C_{in}) were determined. $\Theta_{dextran}$, radii 22-30Å, exceeded unity in 16 patients (15 subsequently required dialysis) and was attributed to inulin backleak through necrotic tubules (ATN). The remainder (n=14) had prerenal failure (PRF) and recovered spontaneously. Using a mass conservation model which assumes glomerular permeability to dextran and inulin to be identical in the two groups, $\Theta_{dextran}$ in PRF (radii 22-30Å<1) was used to estimate fractional backleakage of inulin (K_{in}) in each patient with ATN; and corrected GFR calculated from $C_{in} x 1/(1-K_{in})$. On average, this value was not different to C_{in} in PRF, 15±2 vs. 18±2 ml/min/1.73m^2 respectively. Results (mean±SE) for TS and TR were: V=urine flow and *=p<.005

	$V_{ml/min}$	U/P_{in}	$\Theta_{Na} x 100$	Θ_{PAH}	Θ_K
PRF	1.0±0.2	25±4	0.6±0.1	7.1±1.0	0.8±0.1
ATN	1.6±0.3	9±1*	5.1±1.5*	7.1±0.6	1.6±0.2*

Assuming the "worst case", i.e. no PAH or K backleaked in ATN [$\Theta+1/(1-K_{in})$], corrected Θ_{PAH} was 5.3±.3 and Θ_K=1.2±.2 (p=0.07 vs. unity). Thus GF and TS in both the proximal and terminal tubule are preserved in non-oliguric ATN relative to PRF. TR for water (low U/P_{in}) and N_a (high Θ_{Na}), however, is impaired. We suggest that impaired TR offsets loss of tubular fluid by backleak and accounts for high urine flow in non-oliguric ATN.

PROTECTION FROM ACUTE RENAL FAILURE (ARF) BY ENDOTOXIN (E) DESENSITIZATION. A.I. Jacob, G. Bourgoignie*, J.J. Bourgoignie. Univ. of Miami School of Medicine, Miami, Florida.

ARF is a serious complication of sepsis. E is the major component of the cell wall of gram-negative bacteria and will cause ARF in rats when injected in high doses (7.5-40 mg/kg i.v.). We have separately studied the effect of two potentially protective maneuvers, desensitization and acute volume expansion, on the course of endotoxemic ARF. Rats were given progressively larger i.p. doses of E daily for six days, followed by a challenge with 40 mg/kg I.V. Another group of rats were saline expanded (10% body wgt) immediately before E (20 mg/kg i.v.).

	C_{inulin} ml/min/100 gm		
	Control	60-90 min	180-210 min
Sham	1.28	1.05	1.15
E(40 mg/kg)	1.08	.59*	.43*
Desensitized + E	1.14	.74	1.10
E(20 mg/kg)	1.08	.47*	.56*
Expanded	1.24	.87	.72*

*p<.01 vs sham

Whereas E caused ARF, prior volume expansion offered slight but only transient protection. In contrast, prior desensitization completely prevented endotoxemic ARF. In separate experiments rats desensitized to endotoxin were also protected from $HgCl_2$-induced ARF (serum creatinine 48 hrs after $HgCl_2$, 1.0 mg/dl vs 4.0 mg/dl in controls (p<.05).

In conclusion, volume expansion is not protective of endotoxemic ARF but desensitization protects from endotoxemic and $HgCl_2$-induced ARF. The mechanism of protection may be broadly relevant to all types of ARF.

EFFECTS OF CIS-PLATINUM (CP), MERCURIC CHLORIDE (HG) AND GLYCEROL (G) ON PROTEIN BOUND SULFHYDYL GROUPS (PB-SH) DURING ACUTE RENAL FAILURE (ARF). Bruce A. Kaiser,* Hendrik J. Vreman,* & Michael W. Weiner, (intr. by Eddie S. Moore). Stanford Univ., VA Med. Ctr., Palo Alto, Ca. & Michael Reese Hosp., Chicago, Ill.

The use of CP, an important chemotherapeutic agent, is limited by its nephrotoxicity. The mechanism of CP toxicity is unknown. However it has been postulated that the nephrotoxic effect of CP is similar to that of other heavy metals. Mercury, the most studied of the metals, is believed to cause ARF through an interaction with PB-SH. To evaluate this postulate we compared the changes in PB-SH (umoles/mg protein) in rat kidneys after a single dose of either CP (12mg/Kg), or Hg (2mg/Kg) or 50% G (10cc/Kg) was given to an experimental group. At 24 hours after exposure to CP or HG or G, the PB-SH (expressed as % of a control group) were 101% (p=ns), 73% (p<0.001) and 91% (p<0.01) respectively. However, at 24 hours the BUN of the CP group was only 28±2 mg% compared to 131±22 mg% for Hg and 167±19 mg% for G. At 72 hours after exposure the PB-SH of the CP group fell to 81% of control (p<0.02) and the BUN rose to 180±61 mg%. However, the PB-SH of the G group also fell to 81% of control at 72 hours. Thus CP induced ARF more slowly than HG or G and caused a decrease in PB-SH that was less severe than Hg and similar to G. These results imply the CP nephrotoxic effect is not solely related to an interaction with PB-SH.

ROLE OF RATE OF K ADMINISTRATION, PLASMA K AND BETA ADRENERGIC BLOCKADE ON EXTRARENAL K TRANSFER. D.M. Kaji, A. Sugarman*, R.M. Stein, M. Wadhwa*, J. Torelli*, T. Kahn. V.A. Medical Center, Bronx, NY and Mount Sinai Medical School, New York, NY.

Studies were performed to evaluate the effects of the rate of K administration, plasma K (P_K) and the beta adrenergic system on the transfer of K out from the ECV. Acutely nephrectomized rats were infused with KCl 1.25, 2.50, or 3.75 μEq/100g/min and observed up to 60 min. following the discontinuation of the infusion. Similar studies were performed in the presence of butoxamine, a beta-adrenergic blocking agent. ECV space (by [^{3}H] inulin) remained relatively stable throughout all studies.

Infusion Rate	K Transfer μEq/min/100 gms Without B Blockade			With B Blockade		
μEq/min/100g	30"	60"	90"	30"	60"	90"
KCl 1.25	0.79	0.88	0.85	0.58	0.62	0.86
KCl 2.50	2.01	1.89	2.00	1.45	1.63	1.97
KCl 3.75	2.75	2.93	3.16	2.20	2.62	-

The rate of K transfer increased with increasing rates of administration but remained relatively constant at a given rate in spite of a rising P_K. Stopping K infusion resulted in a steep fall in K transfer (not shown) despite persistent hyperkalemia. Beta blockade without KCl resulted in a progressive rise in P_K (1.06 mEq/l at 90 min). Beta blockade with KCl resulted in a greater rise in P_K and diminished rate of transfer as compared to KCl alone. Despite beta blockade, increasing rate of K administration resulted in a progressively greater K transfer. Conclusions: The rate of K administration is a more important determinant of K transfer than P_K. The beta adrenergic system plays an important role in modulating basal P_K. Increasing rates of K administration result in progressively greater K transfer despite beta blockade.

DISPOSITION OF ORAL POTASSIUM (K) IN DOGS WITH CHRONIC RENAL INSUFFICIENCY. M. Kaplan, J. Pincus, G. Gavellas* and J.J. Bourgoignie. Univ. of Miami School of Medicine, Miami, Florida.

Controversy exists on the ability of the diseased kidney to excrete K. We, therefore, examined the dynamics of K excretion in 6 normal dogs and 18 dogs with chronic renal insufficiency of at least 4 wk duration (remnant model). All animals, in balance on diets providing 15, 50 or 100 meq K and 100 meq Na were challenged orally with 50 meq KCl. Immediately thereafter, they were studied hourly for 5 hours. Irrespective of dietary K, fasting serum K and U_KV were similar in normal and remnant dogs with mean GFR's of 57 ± 3 and 16 ± 3 ml/min respectively. After orogastric administration of 50 meq K, serum K rose significantly more (2.1 vs 0.9 meq/L) and U_KV significantly less (90 vs 200 μeq/min) in remnant than in normal dogs ($p<0.001$). In 5 hours the normal animals excreted 61-67 percent of the load and the remnant dogs only 30-37 percent ($p<0.001$). In all groups, U_KV correlated directly with serum K concentration. However, this relationship was markedly attenuated in the remnant groups ($p<0.001$) and was independent of dietary K. In contrast, the same slope describes the relationship between serum K and U_KV/GFR for all, normal and remnant, animals. After the challenge, the severe hyperkalemia in remnant dogs occurred despite an apparent increase in tissue buffering of K and was not associated with significant changes in plasma insulin and glucagon levels. These results demonstrate a severe limitation of the remnant kidney's ability to excrete K. Serum K, or a consequence thereof, is an important mediator of K excretion following its acute administration.

● INCREASED UREA PRODUCTION IS A MAJOR FACTOR IN THE AZOTEMIA OF DIURETIC INDUCED SODIUM DEPLETION(NaD). D.E.Kamm, L.Wu*, B.Kuchmy*. Roch. Gen. Hosp., Univ. Roch. Sch. Med., Rochester, New York 14621

The azotemia commonly seen during diuretic therapy is usually attributed to a decrease in urea clearance (C_U). These experiments examine the relation of C_U and urea appearance (UA) (U excretion + Δ total body U) to plasma [U] (PU) in rats given furosemide (25-40 mg·kg^{-1}·d^{-1})for 3 days. Group I was tube fed a 10% dextrose solution (30ml/d) containing only replacement KCl (NaD) and Group 2 the same solution plus replacement NaCl (NaR). Compared with the preexperimental value of 17±.4 mg·dl^{-1}, PU increased significantly in NaD ($p<0.01$), an effect largely prevented by Na repletion. (Table)

	PU	C_{Creat}	C_U	UA	Na Bal
NaR	28±2	.98±.1	.15±.01	166±6	56±28
NaD	60±5*	.78±.04†	.11±.02^{NS}	245±13*	-831±42*

Compared to NaR, NaD had a decrease in $C_{creatinine}$ and C_U (ml·min^{-1}·100GBW^{-1}), an increase in UA (mg·3d^{-1}·100GBW^{-1}), negative Na and K (-231±35 vs. -57±24 $p<0.01$)balance (μEq·3d^{-1}·100GBW^{-1}), greater weight loss (10±0.6%/3d^{-1} vs. 6.8±0.5 $p<0.01$),insignificant decreases in plasma [Na] (127±2 mEq·L^{-1} vs. 132±3) and [CO_2] (17±1.5 mM vs. 19.3±1), and an increased plasma [K] (4.7±.2 mEq·L^{-1} vs. 4.0±.1, $p<0.01$). UA correlated negatively with Na balance ($r=0.82$, $p<0.01$). UA also increased ($p<0.01$) in NaD, in an experiment where NaD received less K (K bal -328±38) and had a plasma [K] (4.23±.12) similar to NaR (4.03±.12). Conclusion: In the rat a fall in C_U accounts for only 30% of the elevation in plasma [urea] found during furosemide treatment; the bulk of the increment in plasma [urea] is secondary to enhanced urea appearance.
Significantly different from NaR $p<0.01$*, <0.05†.

MECHANISM OF HYPOALBUMINEMIA IN UREMIC RATS. G. Kaysen, and J. Watson* Univ. of Calif. Renal Center, San Francisco General Hosp., San Francisco, CA.

To study the mechanism of hypoalbuminemia in uremia, Sprague Dawley rats were 7/8 nephrectomized. Uremic animals, (BUN 66.6±28 vs 17.4±3.7 mg%) had a significantly reduced plasma albumin (Alb) concentration, (17.8±2.4 vs 21.7±1.76 mg/ml $p<.001$) and a significantly reduced plasma volume (PV) (4.42±1 vs 3.46±.66% body wt. $p<.001$). Plasma albumin mass (PAM) and total body Alb. mass were the same in both groups, despite significant proteinuria in the uremic group (1.83±.67 vs .107±.132 mg/100g body wt/hr $p<.001$). Alb. synthesis was increased (4.60± 1.15 vs 2.17±.72 mg/100g body wt/hr $p<.001$). It seemed uremic rats maintained a constant PAM and dropped Alb. concentration only secondary to PV expansion. To test this hypothesis, rats were rendered uremic but volume expansion was prevented by feeding the rats a low salt diet from the time of nephrectomy. The uremic animals maintained a serum Alb. concentration, (21.29±1.42 vs 22.44± 1.24 mg/ml, PV 3.46±.35 vs 3.35±.17% body wt and PAM 71.3±4.4 vs 76.9±6.37 mg/100g body wt) that was the same as control. When the animals were fed a standard (high salt) diet, uremic rats reduced plasma Alb. concentration (17.05±1.8 vs 19.03±1.05 mg% $p<.05$) increased PV (4.0±.22 vs 3.51±.27% body wt $p<.01$), and maintained constancy of PAM (71.73± 4.86 vs 66.7±6.32 mg/100g body wt.)

PAM is maintained in uremic rats despite proteinuria, and hypoalbuminemia is avoided, if PV expansion is prevented. Given a normal salt intake, uremic rats will expand PV and decrease serum Alb. concentration but will maintain constant PAM. Homeostasis seems to guard Alb. pool mass more effectively than it does plasma Alb. concentration.

DISTAL CHLORIDE DELIVERY DURING THE DEVELOPMENT OF TOXIC ACUTE RENAL FAILURE IN THE RAT. P.E. Klotman,* W.J. Newman,* and W.E. Yarger. Duke University Med. Ctr., Dept. of Med., Durham, NC

To determine whether distal tubular chloride (Cl) delivery (DClD) is increased during the development of toxic acute renal failure (ARF), salt depleted rats were treated with gentamicin, 100 mg/kg/day (G) or its solvent vehicle (C) for 24 or 48h. After 48h both GFR and CPAH are decreased by G. After 24h (see Table) GFR (ml/min/kg) is

	GFR	CPAH	PNFR	DNFR	PTF/P	PCl	DTF/P	DCl	DClD
G	6.86	18.5	161.	148.	2.53	136.	5.89	44.0	1141
C	7.12	25.5	171.	150.	3.42	154.	7.66	60.3	1219
P	NS	<.01	NS	NS	<.01	<.01	<.01	<.01	NS

unchanged although CPAH is reduced. Nephron filtration rates (nl/min/kg) measured in proximal (PNFR) and distal (DNFR) tubules are not altered by G although PNFR tend to be higher than DNFR in both groups. Fractional reabsorption of the glomerular filtrate, indicated by the TF/P inulin, is decreased by G at both end proximal (PTF/P) and early distal (DTF/P) tubular sites. Likewise the concentration of Cl (mEq/l) is decreased by G at both end proximal (PCl) and distal (DCl) sites although the absolute delivery of Cl (nEq/min/kg) to the distal tubule is not changed.

In conclusion: 1) In this model of ARF at a time when GFR remains normal and CPAH, and presumably, RBF are slightly decreased, neither the concentration nor the absolute amount of Cl delivered to the early distal tubules are increased. 2) The slightly increased rates of PNFR vs. DNFR suggest that glomerulo-tubular feedback is intact. A role for increased distal chloride in the genesis of ARF is not confirmed, although increased volume or other solutes may be important.

● ALTERED SKELETAL CYCLIC AMP (cAMP) RESPONSE TO PARATHYROID HORMONE (PTH) IN GLUCOCORTICOID (GC) TREATED DOGS. A. Korkor*, E. Bellorin-Font, K. Martin, S. Teitelbaum, K. Olgaard, J. Schwartz*, D. Finco, M. Fallon*, S. Klahr, and E. Slatopolsky. Washington Univ., St. Louis, MO.

Chronic GC therapy is used frequently in the management of patients with glomerular disease and renal transplantation. Osteopenia is a common complication of such therapy. This study was designed to examine the effects of GC administration in vivo on: 1) cAMP release by the isolated perfused dog tibia before and after the addition of b-PTH 1-34 to the perfusate in vitro and 2) the % extraction of b-PTH 1-34 (%PTH Ext.) by bone. Two groups of adult mongrel dogs were studied. Group 1 (n=7) received a single injection of methylprednisolone (MP) 6 mg/Kg intravenously and Group 2 (n=9) received oral prednisone 3 mg/Kg daily for 4 weeks. At the end of treatment period (5 hrs for Group 1 and 4 weeks for Group 2) the dogs were killed and the tibiae were removed and perfused in vitro. In control untreated dogs cAMP increased from 6.9 ± 1.6 to 23.3 ± 2.6; in Group 1 the rise was from 6.1 ± 1.2 to 39.2 ± 4.0, and in Group 2 from 3.1 ± 0.4 to 11.8 ± 0.4 pmol/min. % PTH Ext. was the same in all groups. In dogs of Group 2 histologic studies were obtained and revealed osteopenia and suppressed bone resorption and formation parameters. Thus: 1) acute administration of MP in vivo enhances the response of bone to parathyroid hormone; 2) chronic prednisone therapy resulted in decreased basal and PTH-stimulated cAMP release, an effect which correlated with histologic evidence of decreased bone cell activity; 3) acute or chronic administration of GC did not affect %b-PTH Ext. by the bone.

THE JEJUNAL TRANSPORT OF Na and K IN MODERATE CHRONIC RENAL FAILURE. Tatsuhara Kobayashi*, Burton P. Fine* and Abraham Aviv. New Jersey Medical School, Div. of Ped. Nephrol., Newark, New Jersey.

Previous studies indicated that in the rat with a "mild" chronic renal failure (CRF) there was a substantial change in the transport of Na and K by the colon. Yet, under the same conditions, no change was observed in the jejunal transport of these electrolytes (Bastl et al, K.I. 12, 9-16, 1977). The present study examines the jejunal transport of these ions under conditions of a more profound CRF. Sprague-Dawley rats underwent subtotal nephrectomies and were studied two weeks after induction of CRF; BUN 95 ± 5 mg% (mean ± SEM). Animals with CRF feed poorly and their potassium intake diminishes. Therefore, CRF animals were compared with sham-operated rats pair-fed with the CRF group (SI), and sham-operated rats fed ad lib (SII). This approach made it possible to distinguish jejunal transport change in CRF from the effect of malnutrition. The transport studies were conducted using in-vivo intestinal perfusion techniques. There were no demonstrable differences in the jejunal transport of Na between the CRF and the sham-operated groups. Significant differences in the net jejunal K absorption between the CRF group and the sham-operated groups were observed. The following results are expressed as nEq of transported K per cm of perfused jejunal segment per minute: CRF 0.4 ± 0.9 as compared with SI 3.9 ± 1.5 ($P<0.05$) or in comparison with SII 6.1 ± 2.6 ($P<0.01$). It is theorized that under profound CRF the jejunum manifests alteration in potassium transport that may represent an adaptive process at the time when the potassium excretion by the residual renal tissue approaches its maximum.

SEARCH FOR A CIRCULATING FACTOR IN MYOHEMOGLOBINURIC ACUTE RENAL FAILURE. Kenneth M. Kornetsky, Bruce Jackson and Donald E. Oken, Departments of Medicine, Medical College of Virginia and Veterans Administration Hospital, Richmond, Virginia.

It is not known whether sustained filtration failure in acute renal failure (ARF) is caused by local or circulating factors. Accordingly, normal rats were cross circulated for up to 5½h with animals injected with 50% glycerol 24h earlier (N x ARF), or with other normals (N x N). Inulin clearances (C_{IN}) were measured in each rat, and cross circulation was achieved with the rats awake using a self adjusting automatic pump system set at 1 ml/min. N x N cross circulation produced no significant change in C_{IN} (control 2.51±SE 0.31 ml/min, cross circulated 2.28±0.26 ml/min, paired $t=0.985$, $p>0.3$). N x ARF exchange left C_{IN} unchanged in both N (C_{IN} 2.06±0.21 ml/min vs 2.22±0.18 ml/min) and ARF rats (0.24±0.08 ml/min vs 0.21±0.18 ml/min, $p>0.5$). If a circulating factor is responsible for myohemoglobinuric ARF: a) it is present in insufficient titer to impair GFR of cross circulated normal rats b) cross circulation with normal animals at 1 ml blood per minute does not remove this substance sufficiently to ameliorate GFR in rats with ARF. The results favor a local, rather than a humoral, basis for the maintenance phase of this model of acute renal failure in rats.

RENAL CORTICAL AMINO ACID CONCENTRATIONS IN EXPERIMENTAL ACUTE RENAL FAILURE. Nouhad Kronfol, Maria A. Duran*, Patricia Spencer*, Manfred Weise* and Donald E. Oken. Dept. of Medicine, Medical College of Virginia, Richmond, Virginia.

If proximal tubular permeability permits indiscriminate back leakage in acute renal failure (ARF), cellular gradients for amino acids (AA) should be dissipated. Accordingly, renal cortical and serum AA concentrations were measured in control rats and animals with established glycerol induced ARF to serve as an indicator of pathologic tubular permeability. Renal interstitial volume (ECF) was measured with ^{14}C inulin, cell H_2O was determined from total tissue H_2O and ECF. AA concentrations were measured by conjugation with ^{14}C dansyl chloride and thin layer chromatography. Cellular AA were derived from total free tissue AA content minus the product of ECF and plasma AA concentration. Lysine concentration (μMole/Kg H_2O) in serum of ARF rats fell from 534±SEM to 358±25 ($p<0.02$), isoleucine rose from 85±9 to 98±8 ($p<0.02$), and threonine rose from 237±27 to 685±78 ($p<0.01$). Concentrations of the other 14 serum AA measured were not different from control. In cortical tissue, glutamate concentration (μMole/Kg cell H_2O) fell from 15,302±1,164 to 12,328±538 ($p<0.05$), threonine fell from 2,836±241 to 1,614±385 and serine fell from 6,531±799 to 2,804±385 ($p<0.01$). The tyrosine concentration rose (1,656±172 vs 1,225±89, $p<0.05$). The other cellular AA were unchanged. Even those AA showing a fall in tissue still maintained mean cell water:serum concentration ratios of 2.4 (threonine) to 52.2 (glutamate). It is concluded that pathologic tubular permeability does not attend myohemoglobinuric ARF in the rat.

MAGNESIUM (Mg) ADAPTATION IN DOGS WITH REDUCED RENAL MASS. B. Liebross*, A.Lowe*, N.Bricker, M.Kirschenbaum Div. of Neph., UCLA Sch. of Med., Los Angeles, CA.

Reduction of nephron mass is accompanied by homeostatic responses which maintain constant ECF concentrations of numerous solutes. These studies evaluated whether similar adaptations occur for Mg. Awake dogs on both normal and 0 Mg diets were studied in the AM following an 18 hr fast and then 1 hr after an IV Mg load (Stage I) or after 7/8 nephrectomy (Stage III).

Stage	Mg diet	18 hour fast				1 hr post Mg load			
		UF_{Mg}	GFR	$\frac{U_{Mg}V}{GFR}$	FE_{Mg}	UF_{Mg}	GFR	$\frac{U_{Mg}V}{GFR}$	FE_{Mg}
		μg/ml	ml/min	μg/ml	%	μg/ml	ml/min	μg/ml	%
I	nl	9.6	87	0.18	3.7	34.5	88	14.5	56
I	0	6.8	74	0.04	0.8	34.5	68	34.4	146
III	nl	12.8	18	2.35	18.5	34.9	16	47.7	151
III	0	9.7	15	0.10	0.9	29.9	14	32.0	106

(UF=ultrafilterable and FE=fractional excretion)

The results show that Stage III dogs 1) have higher basal levels of UF_{Mg} and 2) are equally capable of conserving Mg maximally on 0 Mg diet when compared to normal dogs. After an 18 hr fast $U_{Mg}V/GFR$ in Stage III on normal Mg diet was >13X that in Stage I. If corrected for the probable increase in single nephron (SN) GFR in Stage III, the change was still 4X as great. Following an acute Mg challenge net secretion was shown with FE_{Mg} >100% in dogs in all groups. On normal Mg diet peak $U_{Mg}V/GFR$ in Stage III was >3X that in Stage I. However the unadapted dogs (i.e. on 0 Mg diet) showed no increase in $U_{Mg}V/GFR$ in Stage III v. I. Thus Mg adaptation occurs in Stage III animals by virtue of enhanced tubular secretion (or perhaps decreased reabsorption) and by elevation of levels of UF_{Mg}.

PRESSOR EFFECT OF INDOMETHACIN DUE TO INHIBITION OF PROSTAGLANDIN SYNTHESIS IN ANEPHRIC MAN. Bruce R. Leslie, Alicia Terragno*, Alan L. Blumberg*. New York Hospital-Cornell Medical Center, New York, N.Y. and Department of Pharmacology, New York Medical College, Valhalla, N.Y.

Indomethacin (Indo) was used to inhibit prostaglandin synthesis in anephric humans in order to evaluate the role of extra-renal prostaglandins in the regulation of arterial blood pressure. Two anephric patients with symptomatic chronic hypotension received 2 weeks of oral Indo (150 mg/day) bracketed by 2 weeks of either no treatment or placebo control (C). Prostaglandin concentrations in arterial blood were measured by radioimmunoassay. Supine (Sup) and standing (St) blood pressures were measured thrice weekly and mean arterial pressure (MAP) was calculated. Indo increased MAP (mm Hg, mean ± SD) in both patients:

Patient	C		Indo	
	Sup	St	Sup	St
1	45.6±2.0	46.0±4.1	57.4±4.7	60.7±7.0
2	62.5±5.5	76.6±6.6	78.1±5.3	89.3±9.4

(Indo vs. C, $p < .02$)

Weights were constant. Symptoms were abolished. The increases in blood pressure were associated with decreases in prostaglandin concentrations (pg/ml blood):

Patient	6-keto-$PGF_{1\alpha}$		PGE_2		$PGF_{2\alpha}$	
	C	Indo	C	Indo	C	Indo
1	157.5	97.5	62.5	5.8	11.0	2.9
2	125.0	41.6	19.4	1.4	6.9	3.9

The results suggest that excessive production or decreased degradation of prostaglandins may reduce blood pressure. Prostaglandin synthesis inhibitors may be useful in treatment of prostaglandin-dependent hypotension in anephric patients.

ARSENIC INTOXICATION - A CONTRIBUTION TO ANEMIA IN CHRONIC RENAL FAILURE? Lars-Eric Lins*, Robert Hast, Kenneth Pehrsson and Göran Pershagen. Karolinska Hospital, Dept of Medicine, Stockholm, Sweden.

The primary etiological factor in the anemia in chronic renal failure is probably erythropoetin deficiency, but other factors e.g. hemolysis and inhibition of the heme synthesis in bone marrow are considered to be important factors. Uremic toxins have been discussed as a cause to both hemolysis and inhibition of the heme synthesis. Arsenic could be such a toxin agent. Previous studies have shown high concentrations of arsenic in blood in uremic patients and it is known that arsenic can induce anemia. We have found increased levels of arsenic in bone marrow in 5 non-dialyzed uremic patients with neutron activation analysis (median 70 range 36-89 ppb) compared to 5 controls (median 18 range 13-25 ppb).

The increased concentration of arsenic in the uremic patients suggests an accumulation in bone marrow that might contribute to the inhibition of the heme synthesis.

PARTIAL PROTECTION BY MANNITOL AGAINST GENTAMYCIN INDUCED ACUTE RENAL FAILURE IN RABBITS. B. Louis, P. Gorfein, J. Shani and H. Lipner. Maimonides Medical Center, Div. of Nephrology, Bklyn., N.Y.

Nephrotoxicity is a well known complication of gentamycin (G) administration. Mannitol (M) can protect the kidney against ischemic acute renal failure. In order to evaluate the effect of (M) in (G) nephrotoxicity, 4 groups of 10 New Zealand white rabbits were studied.

Group I Low Dose Gentamycin (LD-G) 7.5mg/Kg TID
Group II LD-G + 25% mannitol - .4cc/Kg.
Group III High Dose Gentamycin (HD-G) 40mg/kg BID
Group IV HD-G + mannitol.

Animals were studied until development of renal failure (serum creatinine 3 x control period) or for a maximum of 28 days.

In Groups I and II renal failure did not develop after 28 days of (G). Renal failure occurred in both Group III and Group IV but serum Cr was significantly lower in Group IV (2.29mg/dl) than in Group III (5.57mg/dl) on day 4. Also, in Group IV animals urine output was significantly greater, fractional excretion of Na and urinary Na concentration were significantly less than in Group III.

Renal cortical concentration of (G) was very high in both Group III (2129.4mcg/Gm of kidney tissue) and in Group IV (2066.5mcg/Gm) but were not statistically different from each other.

Myeloid bodies were seen on EM in the tubules of all 4 groups.

It is concluded that (G) in high doses causes nephrotoxicity in rabbits. (M) has a partial protective effect against (G) nephrotoxicity. Renal lesions occur even in the absence of overt toxicity. The protective effect of (M) occurs in the presence of high cortical (G) concentrations.

REVERSAL OF THE SPLENECTOMY PROTECTION AGAINST ACUTE RENAL FAILURE BY INDOMETHACIN. Anil K. Mandal, M.D. and Francisco Llach, M.D., VAMC and Univ. of Okla., Okla. City, Okla.

We reported that chronic splenectomy protects against epinephrine-induced acute renal failure (ARF), and the protection may be mediated via prostaglandins (PGs). This report describes renal hemodynamic and histopathologic studies during epinephrine infusion (Epi) (4 μg/kg/min for 6 hr.) in indomethacin fed (100 mg daily for 4 days) 7 intact dogs (Group I) and 7 chronic splenectomy dogs (Group II). Kidneys were fixed for light and electron microscopy (LM, EM, respectively). Acute tubular lesions (ATL) were scored on a scale of 0 to 4+. Hemodynamically, there was no significant difference between groups. The 6 hr. means + SEM; Group I vs Group II; urine volume (.02 + .01 vs .11 + .07 ml/min), glomerular filtration rate (1 + .8 vs 18 + 11 ml/min), effective renal plasma flow (2 + 1 vs 42 + 26 ml/min), renal blood flow (flow probe) (114 + 35 vs 127 + 44 ml/min), urinary sodium excretion (.6 + .4 vs 3 + 2 uEq/min) and serum urea nitrogen (32 + 3 vs 29 + 3 mg/dl). LM showed no difference in the severity of ATL between groups. EM showed striking difference in the renal tubules; Group I had amorphous matrix in mitochondria with a few lipid droplets (PGs precursor) while Group II revealed fine granules in mitochondria but numerous similar lipid droplets. Mitochondrial inclusions signify ischemia and lipid droplets suggest PGs storage. Thus, this study confirms our previous observation and provides additional evidence in support of PGs mediating renal protection in chronic splenectomized animals.

NERVOUS SYSTEM EFFECTS OF CHRONIC RENAL FAILURE IN DOGS. C.A. Mahoney,* D.K. Armstrong,* and A.I. Arieff.* Dept. of Medicine, V.A. Med. Ctr. and U.C.S.F., San Francisco, California.

Effects of chronic renal failure (CRF) on function and chemical composition of the nervous system have not been well studied. CRF was induced in dogs by 1-7/8 nephrectomy (GFR<10 ml/min) for periods of 4 days to 6 mos. Studies were made of the EEG, and in brain of intracellular pH (pHi) and content of Na, K, Cl, H_2O, Ca and Mg. Ca was measured in 8 different parts of the brain. In nerve, serial measurements were made of Na, K and Ca, and weekly evaluation of motor nerve conduction velocity (MNCV). In brain cerebral cortex, content of H_2O, Na, K, Cl, and Mg were normal after 6 mos of CRF. Ca was normal in white matter, pons, medulla, cerebellum, thalamus, caudate and hypothalamus. In cortex, Ca was 466±110 mg/kg after 3 wks and 419±40 mg/kg after 6 mos, of CRF (normal value = 287±27 mg/kg, ($p<.01$). With arterial pH of 7.25±0.04, the brain pHi with CRF was 7.03±0.04 (normal = 7.04±0.02, NS). The EEG was grossly abnormal, with % Freq < 7 Hz=56 ±5% (normal = 19±4%, $p<.01$) and % power < 5 Hz=47±5% (normal = 4±5%, $p<.01$). In peroneal nerve, the MNCV was 60±7 M/sec at 4 days, 62.6±6 M/sec at 3 wks and 65±4 M/sec at 6 mos (normal = 63±4, NS). With renal failure, nerve Ca was 245±17 mg/kg after 4 days, 290±27 mg/kg at 3 wks, and 226±18 mg/kg after 6 mos (normal = 348±28 mg/kg, NS).

Conclusions: In dogs with CRF the nervous system maintains remarkable homeostasis: 1) there are no detectable changes of nerve function or composition for up to 6 mos; 2) brain pHi, H_2O, Na, K, Mg and Cl are normal; 3) in brain after 4 days to 6 mos, Ca is normal in 7 parts of the brain but elevated in cortex, while EEG is normal.

VASCULAR FUNCTION AND VASCULAR HISTOLOGY IN ISCHEMIC ARF. E. Matthys,* M. Patton,* R. Osgood,* J. Stein and M. Venkatachalam. U. of Tx. Hlth. Sci. Ctr., Depts. of Med. and Path., San Antonio, Tx.

Degenerative vascular lesions have been described in ischemic renal injury, (Amer. J. Path. 58, 69-83, 1970) and may underlie altered vascular function. Renal autoregulatory function and histology were examined in rats (320-375gm), 48 hours (n=5) and 7 days (n=9) after clamping the left renal artery for 40 minutes. Sham operated rats (n=4) served as controls. At 48 hours, all clamped kidneys were anuric. The renal blood flow (RBF) at a renal perfusion pressure (RPP) of 110 mmHg was not significantly different from the control rats (5.94 ± 0.62 ml/min vs. 5.35 ± 0.55 ml/min). At that time, all rats had lost their autoregulatory capacity. At 7 days, two groups were observed: a group (n=4) with normal autoregulation and a group (n=5) with persistent loss of autoregulation. RBF at a RPP of 110 mmHg in the second group was significantly lower than in the first group (3.62 ± 0.73 ml/min vs. 5.30 ± 0.24 ml/min; $p<0.05$). Both groups showed severely depressed GFR. Loss of autoregulation at 48 hours was accompanied by severe vascular injury. The lesion was characterized predominantly by necrosis of the interlobular arterial and glomerular arteriolar smooth muscle cells. At 7 days, necrosis was not observed, but interlobular arteries and glomerular arterioles showed vascular fibrosis. However, the degree of vascular fibrosis could not be quantitated with accuracy and correlation with autoregulatory function was not possible. Renal tubular and interstitial histology was not different between the two groups at 7 days. Sham operated rats showed normal renal function, autoregulation and histology.

The results suggest that vascular pathology may account for altered renal vascular function, at least at 48 hours after induction of ischemic ARF.

THE EFFECT OF BENZOATE (B) ON UREA METABOLISM OF PATIENTS WITH CHRONIC RENAL FAILURE (CRF). W.E. Mitch and S.W. Brusilow*, Dept. of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Mass. and Dept. of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Md.

It has been demonstrated that amino acid acylation can serve as a means of excreting waste nitrogen by children with abnormal ureagenesis. For example, B acylates glycine to form hippurate whose renal clearance exceeds GFR even in CRF. The possibility that urea accumulation in CRF could be diminished by this pathway was examined in 7 patients with an average estimated GFR of 7.8 + 1.3 (S.E.) ml/min. A control period of 5-7 days of constant nitrogen intake was compared to an identical period in which 10 g/d of B was given orally. Control nitrogen balance (bN) of .08 + .39 was increased by 1.29 + .35 gN/day when B was taken. Serum urea nitrogen fell from 89 + 5 to 71 + 4 mg/dL ($p<.001$) as the urea pool decreased by 1.7 + 0.5 ($p<.05$) gN/d. As expected urea appearance, the sum of urea excretion and changes in the urea pool, decreased by 1.34 + 0.37 gN/d ($p<0.02$) when B was given. All 7 patients had an increase in hippuric acid nitrogen excretion (HAN) increasing from a daily average of 0.09 + 0.02 g to 0.73 + 0.07 when taking B. Urine collections were continued in 4 patients after B was discontinued. Cumulative HAN excretion in these patients was 4.69 + .43 gN which is 90% of the theoretical amount of 4.85 if all 50g of B were completely converted to HAN. There was no change in fasting plasma glycine or serine. No adverse effects of B were noted. These results indicate that this amino acid acylation pathway is active in patients with CRF and will divert waste nitrogen from urea synthesis. This results in a fall in SUN while nitrogen intake is constant.

COMPLETE PROTECTION FROM CIS-PLATINUM-INDUCED ACUTE RENAL FAILURE (Pt-ARF) IN THE UNTREATED STREPTOZOTOCIN-INDUCED DIABETES MELLITUS (DM) RAT. J. Morales*, R.B. Teixeira*, J. Kelley*, H. Alpert*, V. Pardo and C.A. Vaamonde; VA Medical Center & Dept of Medicine & Pathology, Univ. of Miami School of Medicine, Miami, Florida

Cis-platinum (Pt) produces ARF in man and animals. Because high renal solute excretion protects against nephrotoxic ARF, we used female Sprague-Dawley (S-D) rats with DM to assess protection from Pt-ARF. Two groups received Pt in a single dose (6mg/Kg) i.p.: a) rats injected with streptozotocin (50 mg/Kg) 9 wks before (DM) and b) age-matched S-D controls (C). Animals were kept in metabolic cages and studied for 6 days after Pt.

	Baseline			Platinum	
	V	Pgluc	Pcr	max Pcr	max ΔGFR
	ml/day	mg/dl	mg/dl	mg/dl	%
DM	115±14 †	585±30 †	.28±.03 †	.35±.05 †	↑ 6±2 †
C	12±1	141±4	.35±.02	2.9±.6*	↓86±7*

$\bar{x}$ ±SE; *p <.001 from baseline, † <.001 from C.

Baseline Ccr, UNaV and Cosm were greater in DM rats ($p<.005$). After Pt, C rats showed a marked decrease in GFR and focal acute tubular necrosis predominantly in proximal tubules. No lysozymuria was detected in C or DM, but, transient glycosuria was seen in C. In marked contrast, DM rats maintained their functional and morphologic integrity.

We conclude that in contrast to the development of ARF in C, complete protection from Pt-ARF was afforded in DM rats. Protection appeared related to their increased solute excretion. The rat with streptozotocin-induced diabetes mellitus constitutes a useful model for the study of platinum-induced nephrotoxicity.

INCIDENCE AND SPECTRUM OF ACUTE RENAL FAILURE (ARF) ASSOCIATED WITH CHELATION TREATMENT (CT) FOR PLUMBISM IN CHILDREN. Donald I. Moel and Kusum Kumar*, State Univ. of New York, Downstate Med. Ctr., Dept. of Pediatrics, Brooklyn, NY.

From 1975-80, 130 children aged 1 to 8 yrs. ($\bar{x}$3.2±0.2 yrs.) with blood lead levels >50 µg/dl whole blood (WB) and free erythrocyte protoporphyrin (FEP) concentration >250 µg/dl packed red blood cells (pRBC) received 207 CT for plumbism. Thirty nine (30%) received multiple courses of CT. All CT consisted of $CaNa_2EDTA$ 25 mg/kg/dose q12h and BAL 3 mg/kg/dose q4h x 5 days. Pre CT blood lead levels ranged between 53-120 µg/dl WB ($\bar{x}$79±1 µg/dl WB) Hgb, 8-13.6 gm/dl ($\bar{x}$11.1±.2 gm/dl) and FEP, (normal <50 µg/dl pRBC) 210-855 µg/dl pRBC ($\bar{x}$382±18 µg/dl pRBC). Seventeen children demonstrated a transient doubling of pre CT serum creatinine (Scr) ($\bar{x}$2.0 mg/dl) during or following CT; 5/17 also had mild proteinuria. In addition 6 developed transient proteinuria (250-500 mg/day for 2-3 days) and 2 glycosuria (.5-.75 g/dl) with no elevation of Scr. Four children developed severe oliguric (<250 ml/m^2/day) ARF. Scr was elevated 6-7 days after CT was started and reached maximal values of 3.9-8.4 mg/dl, 3-6 days later. Renal function returned to pre CT values during the subsequent 6-18 days. In the 21 children who developed biochemical evidence of ARF the mean age (3.8±0.6 yrs.), pre CT lead level (85±5 µg/dl WB, Hgb (11.5±.4 gm/dl), and FEP (380±30 µg/dl pRBC) and per cent who were given multiple courses of CT (41%) did not differ significantly from the general study group. We conclude that 10% of children who receive CT for plumbism develop evidence of reversible renal damage (2% develop severe ARF) and as yet specific risk factors have not been identified.

DIFFERENCES IN THE CONTROL OF GLOMERULAR FILTRATION IN RAT AND DOG. Donald E. Oken, Department of Medicine, Medical College of Virginia, Richmond, Virginia.

Present views on the physiologic control of glomerular filtration rest heavily on glomerular dynamic studies performed on rats. Studies in the dog have shown comparable values for hydraulic conductivity (Kf), serum protein concentration and hematocrit to those of the rat, but afferent (R_A) and efferent (R_E) resistances, total vascular resistance, and net filtration pressure are reportedly significantly different. The consequence of these differences in the control of GFR has been analyzed applying network thermodynamic modeling and the SPICE 2 computer program to experimental values of Brenner et al in the rat and Knox and Navar and their co-workers in dog. Axial net filtration pressure (ΔP) change is linear in the dog, permitting calculation of Kf as the simple mean of afferent and efferent net pressures. In the rat, axial pressure change is curvilinear but not exponential. Increasing the hydraulic conductivity of hydropenic or euhydric rats has almost no effect on GFR, and decreasing Kf by half lowers GFR F10%. In the dog, even small increases or decreases in Kf produce marked changes in GFR. Increasing R_E in the rat produces a maximum increase in GFR of approximately 10%, further increase causing GFR to fall. Doubling R_E in the dog increases GFR by some 25 nl/min. Dog exhibits far greater sensitivity to GFR to change in R_A, proximal tubule pressure and serum protein concentrations than the rat. Thus, physiological/pharmacologic manipulations affecting the individual determinants of glomerular dynamics may have quite differet effects in the two species.

THE EXTRACTION OF PTH (1-34) AND THE GENERATION OF cAMP BY ISOLATED PERFUSED BONES FROM ACUTELY UREMIC DOGS. K. Olgaard, J. Schwartz*, D. Finco, K. Martin, A. Korkor*, E. Bellorin Font, M. Arbelaez*, S. Klahr, and E. Slatopolsky. Renal Div., Washington Univ., St. Louis, MO.

Skeletal resistance to the calcemic effect of PTH has been reported after bilateral nephrectomy (BNX) as early as 5 hrs in rats and 24 hrs in dogs. Although deficiency of $1,25(OH)_2D_3$ and phosphate (PO_4) retention have been implicated as the cause, the mechanisms whereby the effect of PTH on bone is altered remains unclear. We, therefore, examined the effect of BNX parathyroidectomy (PTX) and the combination of BNX-PTX on the uptake of PTH 1-34 and the release of cAMP by the isolated perfused tibia of the dog. Normal dogs were subjected to BNX, PTX or both, and 42 hrs later the tibiae were removed for perfusion. The extraction of PTH was equal in all 3 groups (56% $\pm$ 5 (SE)), not different from control. The total cAMP release in the PTX group was significantly lower than control, but neither BNX nor BNX-PTX groups were different from control. To further evaluate the effect of PO_4 retention on skeletal resistance, the PO_4 concentration in the perfusate was increased from 6 to 12 mg%. PTH extraction did not change, but total cAMP release increased significantly in all groups, suggesting either an inhibitory effect of PO_4 on phosphodiesterase or a stimulatory effect on adenylate cyclase via a decrease in intracellular Ca^{++} concentration. Thus, in acute uremia, skeletal extraction of PTH and cAMP release are not impaired. Therefore, the skeletal resistance to PTH observed in acutely uremic dogs is very likely due to a defect located beyond the generation of cAMP.

RENAL THIONEIN mRNA INDUCTION IN RESPONSE TO CADMIUM. Andre J. Ouellette,* Dana Frederick,* and Ronald A. Malt. Cell Biology Unit, Shriners Burns Inst., Surgical Services, Massachusetts General Hosp., Boston, Massachusetts.

To investigate the molecular basis of cadmium-induced nephropathy, we examined renal thionein mRNA appearance in mice subcutaneously injected with 40 µg $CdSO_4$. Five h after injection, RNA was extracted from kidneys homogenized in 6 M guanidine-HCl. [^{35}S]-cysteine-labeled products of cell-free translation directed by renal mRNA were heated to 80° for 2 min and chromatographed on Sephadex G-75 and on Sephadex G-50. On either column, a prominent peak of radioactivity coded by renal mRNA from Cd^{++}-treated mice was absent from the translation products of control renal mRNA. This polypeptide is judged to be thionein on the basis of its specific induction by $CdSO_4$, its heat stability, its co-elution with cytochrome C and with authentic hepatic and renal ^{109}Cd-thionein, its binding to Thiol-activated Sepharose, its absence from [^{3}H]leucine-labeled mRNA-directed translation products. These results demonstrate that the appearance of renal thionein following cadmium exposure results from increased accumulation of thionein-specific mRNA.

MICROPUNCTURE OF THE UNEXPOSED RENAL PAPILLA *IN VIVO*. Richard E. Oliver,* Denis Roy* and Rex L. Jamison: (intr. by Roy H. Maffly). Division of Nephrology, Stanford University Medical Center, Stanford, California.

Micropuncture studies of the exposed renal papilla have the disadvantage that urine osmolality (Uosm) is reduced after ureteral removal. We therefore prepared 8 rats for micropuncture of a visible collecting duct (CD) at the base and tip of the left papilla through the intact ureter despite peristalsis. Samples were obtained before and after ureteral excision. Intermittent CD flow was noted (Schmidt-Nielsen, Reinking, 12th ASN:60A, 79). Tubule fluid-to-plasma (TF/P)osm rose strikingly from base, 2.81±0.30 (SE) to tip, 5.94±0.48 ($P<0.001$), similar to (U/P)osm of R kidney, 6.17 ± 0.42. After ureteral excision, (TF/P)osm declined slightly at the base, 2.33±0.14 (NS) but sharply at the tip, 3.49±0.30 ($P<0.05$); (U/P)osm of R kidney was unchanged. Corresponding values (±SE) for inulin (In), fractional delivery of solute (FD-osm) and Na (FD-Na) were (*$P<0.05$ for tip vs base):

(n=6)		TF/P In	FD-osm (%)	FD-NA (%)
BEFORE:	Base	93 ± 12	3.28 ± 0.36	0.91 ± 0.12
	Tip	168 ± 33	4.98 ± 2.03	0.26 ± 0.16*
AFTER:	Base	83 ± 7	3.03 ± 0.41	0.66 ± 0.15
	Tip	138 ± 25	2.98 ± 0.46	0.30 ± 0.10*

The results 1) reveal a remarkable contribution (50%) to final Uosm by terminal papillary CD; 2) indicate the effect of ureteral excision is nearly exclusively on the exposed papillary CD and 3) raise the possibility of a mechanical role for the ureter in CD function.

TRACE ELEMENTS IN THE UREMIC HEART. Kenneth Pehrsson and Lars-Eric Lins* Karolinska Hospital, Dept of Medicine, Stockholm, Sweden.

Heart failure is the main cause of death in patients with chronic renal failure. The etiology of the uremic heart failure is still obscure. Many factors are discussed, such as hypervolemia, hypertension, anemia, electrolyte imbalance, ischemic heart disease and uremic toxins. Trace elements depending on renal function for excretion could be such uremic toxins. In a postmortem study of 8 non-dialyzed uremic patients (mean age 63.9) the concentration of 23 trace elements was determined in the uremic heart tissue with neutron activation analysis. The mean or median value and the range of each trace elements was compared to 20 controls. Among these trace elements cobalt is known to be toxic to the heart; especially in connection with low-protein diet. Concentration of cobalt was significant increased in the uremic patients (median 55; range 2-430 ppb) compared to controls (median 12; range 1-18 ppb).

A few other trace elements were also increased e.g. As, Br, Cd, La and Sc. None of these trace elements has, however, been proven to be cardiotoxic, although As has been suspected. These results support our belief that toxic effects of trace elements may be important in uremic patients. In particular, cobalt may be one, or even the prime etiological agent for uremic heart failure.

THE INFLUENCE OF AGE ON URANYL NITRATE (UN) NEPHROTOXICITY. Juan C. Pelayo*, Peter M.Andrews*, Philip L. Calcagno, Gilbert M. Eisner & Pedro A. Jose. Georgetown Univ. Med. Ctr., Dept. of Peds., Med., Physiol. & Biophys., & Anat. Wash. D.C.

The newborn may be more resistant to the nephrotoxic effects of aminoglycosides. To determine if this resistance extends to other nephrotoxins, we studied the effects of UN (10 mg/kg IV) on renal function in dogs 1-2 wks (I) and 3-5 wks (II) of age. Studies were performed 2 hrs and 24 hrs after UN administration.Age matched controls received saline (S). The results (Mean±SEM) are tabulated:

Group I	S n=5	2 hrs n=5	24 hrs n=5
GFR[a]	0.29±0.05	0.24±0.05	0.15±0.04*
RPF[a]	1.74±0.09	1.37±0.16	2.00±0.17
V ul/min	16.60±3.50	26.66±5.56	11.80±4.56
FENa %	1.05±0.40	1.56±0.32	4.60±2.49
Group II	**S n=5**	**2 hrs n=5**	**24 hrs n=5**
GFR[a]	0.31±0.05	0.24±0.06	0.00±0.00*#
RPF[a]	1.73±0.14	1.96±0.20	1.83±0.09
V ul/min	36.15±11.85	29.49±8.19	1.23±0.52*#
FENa %	0.49±0.18	0.58±0.12	36.17±18.63*#

a=ml/min/100 g body wt. *=p<.05 24 hrs vs 2 hrs or S. # = p<.05 I vs II.

Although GFR and RPF were similar for I and II in S glomerular differentiation (light & electron microscopy) was greater in II, consistent with chronological age. 2 hrs post UN, there was extensive vacuolation of the pars convoluta greater in II than in I.Glomeruli and distal tubules were not altered. 24 hrs post UN there were no distinct morphological changes.The paucity of RPF and morphologic changes 24 hrs post UN is in contrast to results in adults.

It is concluded that the young puppy at 1-2 wks is more resistant to some nephrotoxins than the puppy at 3-5 wks and to the adult dog.

EVIDENCE FOR HIGH TOTAL BODY HEME TURNOVER IN DIALYSIS PATIENTS (DP). John M. Pepe*, Rhoda D. Levine*, and Robert E. Longnecker. Baumritter Kidney Center, Albert Einstein College of Medicine, Bronx, New York.

The anemia of renal failure is multifactorial in origin. Inasmuch as the endogenous rate of carbon monoxide production ($\dot{V}CO$) is a quantitative measure of total body heme turnover, its measurement in DP should help clarify the mechanisms of anemia in chronic renal failure.

We studied $\dot{V}CO$ in 6 DP and 3 normal controls using a closed rebreathing system and gas chromatographic analysis.

Patient	Sex	Dialysis	Hb gm%	$\dot{V}CO$ uM/hr.
1	M	HD	11.0	72.2
2	M	PD	10.0	119.7
3	M	HD	10.6	96.0
4	F	HD	6.0	103.8
5	M	HD	10.0	54.1
6	M	HD	8.6	83.6

PD = Peritoneal Dialysis HD = Hemodialysis

In controls $\dot{V}CO$ was 27.6 ± 1.04 SD uM/hr., and in the DP group 88.2 ± 23.4 ($p<.01$ unpaired t test). Interestingly, the patient with the highest $\dot{V}CO$ was receiving 4 10 hr. sessions of PD per week.

One explanation of this data would be an increase in turnover of hepatic enzyme heme. However, this seems unlikely since no patient received drugs known to cause that response. It seems more probable that the increase in heme turnover in DP is due to an increase in red cell production which is not reflected in the peripheral hemoglobin concentration because of red cell breakdown either in the marrow (ineffective erythropoiesis) or in the peripheral circulation.

● FUNCTIONAL PROTEINURIA IN ACUTE EXPERIMENTAL DIABETES: THE RELATIONSHIP TO GLYCOSURIA. J.P. Pennell, M.M. Millard*, M.H. Ashby*. Nephrology Division, University of Miami School of Medicine, Miami, Florida.

Proteinuria is the major abnormality of renal function in rats with experimental diabetes. The relationship between proteinuria and glycosuria was examined in 11 rats with acute streptozotocin-induced diabetes mellitus. Daily excretion of glucose and protein were measured sequentially before diabetes, during 5-37 days of acute diabetes, during 7-14 days of insulin administration by an Alzet^{R} pump, and after pump removal. Induction of diabetes promptly resulted in marked polyuria (78±9 ml/24 hrs, $p<.001$) and glucosuria (6.6±0.7 gm/24 hrs, $p<.001$) while proteinuria quadrupled (from 4.7±0.7 mg/24 hrs to 18.8±1.8 mg/24 hrs, $p<.001$). Insulin treatment ameliorated the polyuria (to 18±2 ml/24 hrs) and glycosuria (to 99±25 mg/24 hrs) and resulted in a concommitant striking decrease of proteinuria (to 8.5±1.2 mg/24 hrs, $p<.001$). After pump removal, polyuria and glycosuria resumed and proteinuria promptly returned to pre-treatment levels (19±2.5 mg/24 hrs, $p<.001$). Decreased proteinuria recurred in 5 rats retreated with insulin after 100 days of diabetes. Assays for lysozymuria were negative. In 6 other rats, inulin clearances measured before (2.5±0.2 ml/min) and after 15-21 days of diabetes (2.6±0.5 ml/min) demonstrated no consistent changes in GFR although similar levels of proteinuria occurred (24±4 mg/24 hrs). These data indicate that proteinuria: (1) develops promptly after induction of diabetes in rats, (2) correlates with glycosuria, and (3) is not associated with either lysozymuria or changes in GFR. We conclude that proteinuria in acute experimental diabetes is of functional origin.

HYPONATREMIA PREDISPOSES TO ACUTE RENAL FAILURE (ARF): EVIDENCE FOR THE IMPORTANCE OF OSMOTIC PRESSURE. Mordecai M. Popovtzer and Hanna Wald.* Hadassah-Hebrew University School of Medicine, Jerusalem, Israel.

To assess the importance of osmotic pressure in the induction of acute renal failure in rats, plasma osmolality was reduced with a water load by 22 ± 2 ($\bar{x}$±SE) mOsm/Kg H_2O prior to a renal insult in the following groups: 1. rats with glycerol-induced ARF, 2. rats with glycerol-induced ARF pretreated with high dietary salt intake, and, 3. rats with postischemic ARF induced by ligation of renal artery. Initial plasma renin activity (PRA) and sequential GFR were measured and a comparison was made between control (C) normonatremic, and experimental (E) hyponatremic rats. GFR in intact rats was 0.810±0.063 ml/min. PRA were 30±9 and 19±6 AIIng/ml/h (p NS) in C and E animals respectively. In group 1, GFR values were, after 24h, in C rats 0.210±0.037 and in E rats 0.048±0.011 ml/min ($p<0.01$), and after 48h, in C rats 0.471±0.067 and in E rats 0.260±0.039 ml/min ($p < 0.01$). In group 2, GFR values were, after 24h, in C rats 0.216±0.03 and in E rats 0.043±0.013 ml/min ($p < 0.01$). In group 3, GFR values were after 24h, in C rats 0.281 ±0.060 and in H rats 0.085±0.022 ml/min ($p < 0.01$), and after 48h, in C rats 0.410±0.085 and E rats 0.172±0.051 ml/min ($p < 0.05$). The results of these experiments show that reduced plasma osmolality predisposes to a more severe impairment of renal function after acute renal insult. This effect is not associated with significant changes in PRA and is not altered by high salt intake. Thus it is likely that reduced osmolality per se may enhance the renal insult in experimental ARF.

AMINOGLYCOSIDE ASSOCIATED STIMULATION OF IN VITRO PARA-AMINOHIPPURATE (PAH) UPTAKE BY RENAL CORTICAL SLICES: CORRELATION WITH HISTOLOGIC SITE OF DAMAGE. George A. Porter, W. Clayton Elliott, Donald C. Houghton, and William M. Bennett. Univ. of Oregon Hlth. Sci. Ctr., Divs. of Nephrol. and Path., Portland, Oregon.

PAH transport in the nephron occurs primarily in the terminal segments of the proximal tubule. Male F344 rats treated with toxic doses of gentamicin (G) and neomycin (Neo) demonstrate stimulation of *in vitro* PAH uptake in cortical slices prior to development of frank renal failure. To search for functional and morphologic correlates, we treated rats with nephrotoxic doses of Neo, G, amikacin (A), tobramycin (T) and dibekacin (D) prior to determining *in vitro* PAH uptake. Renal cortical slices were incubated in Cross and Taggart media with 7.4 x 10^{-5}M PAH at 25° under 100% O_2 for 90 minutes. The opposite kidney was evaluated for histologic evidence of injury.

Drug/Dose	G40	Neo150	A360	T120	D120
N	11	4	4	4	4
Max PAH	137	115	141	137	94
Histology	0	0	0	0	I

"Dose" in mg/Kg/day; "Max PAH" = maximal PAH uptake as % of simultaneous control slices; "Histology" notes cortical region initially showing injury: O=outer and middle, I=inner.

We conclude that, since stimulation of PAH uptake is seen only with nephrotoxic aminoglycosides which initially injure the outer cortex, the presence or absence of PAH stimulation may be related to the site of early nephron injury.

EFFECTS OF WATER IMMERSION ON SODIUM EXCRETION IN CHRONIC RENAL FAILURE BEFORE AND AFTER REVERSING THE ADAPTIVE NATRIURESIS OF UREMIA. B.L. Rever,* G. Danovitch, A. Licht, R. Bowman,* and N.S.Bricker. Nephrology Division, UCLA School of Medicine, Los Angeles, CA.

Epstein and others have shown that water immersion to the neck (WI) in normal subjects results in acute elevation of central blood volume and a marked natriuresis. In uremic patients Epstein et al. have found that the natriuresis per nephron of WI is greatly augmented and follows the dictates of the "magnification phenomenon": The lower the GFR, the greater the increase in fractional Na excretion (FE_{Na}). In the present studies, uremic patients were immersed under two conditions: 1) on a normal salt diet (100-120 mEq/day); 2) following slow reduction of dietary sodium to a mean level of 13 mEq/day. Studies were performed in a metabolic unit; patients were in Na Balance and none was either edematous or volume depleted. In the initial studies, despite the typical adaptive natriuresis before immersion (i.e., mean FE_{Na}, 5.3%), during 4 hours of water immersion, FE_{Na} increased by almost threefold (to a mean of 14.9%). After the adaptive natriuresis was reversed (8-16 weeks), mean FE_{Na} fell to 0.9%. Repeat water immersion increased Na excretion by the "de-adapted" nephrons; but the natriuretic response was markedly attenuated (ΔFE_{Na},2.1%). Thus, in the same patients, at the same GFR, the magnified natriuresis per nephron produced by induction of central hypervolemia appears to represent an acquired change in the responsivity of the volume control system rather than an intrinsic change in the nephrons of the diseased kidney or an essential concomitant of the uremic state per se on the operation of the control system.

EFFECTS OF ACUTE UREMIA ON LIPOPROTEIN LIPASE, INSULIN BINDING AND GLUCOSE OXIDATION OF ADIPOSE TISSUE. J.C. Ransom*, A.S. Garfinkel*, J. Nizky*, M.C. Schotz* and K. Kurokawa (Intr. by K.L. Klein). VA Wadsworth Med. Ctr. & UCLA Sch. Med., Los Angeles, CA.

Hypertriglyceridemia (hyperTGemia) is frequently seen in patients with chronic uremia as well as in acute and chronic uremic animals. Underlying mechanism appears to be defective TG removal catalyzed by extrahepatic lipoprotein lipase (LPL) especially adipose tissue LPL. To gain further insight into cellular events underlying uremic hyperTGemia, we examined effects of acute uremia (24 hrs postnephrectomy) in rats on LPL activity in the adipose tissue and on responses to insulin of isolated fat cells. LPL activity fell in uremia from 7.09 to 3.03 mU/mg protein in adipose tissues and from 39.9 to 17.2 mU/mg protein in isolated fat cells. Also, isolated fat cells from uremic rats released less LPL into the incubation medium, 1.8 vs. 0.4 mU/ml. ^{125}I-insulin binding to isolated fat cells was not different between uremic and control rats at all insulin concentrations tested. Glucose oxidation by isolated fat cells measured by $^{14}CO_2$ production from glucose-1-^{14}C was not different in uremic and control rats. The half-time ($t_{½}$) of TG disappearance from circulation following i.v. TG injection was increased in uremic rats from 14.1±2.82 to 24.5±3.04 min. Data show the specific reduction in the adipose tissue LPL in acute uremia which may be responsible for defective triglyceride removal from circulation. There was no significant change in insulin binding nor in insulin-stimulated glucose oxidation in fat cells in acute uremia, thus no insulin resistance could be demonstrated.

SINGLE DOSE GENTAMICIN NEPHROTOXICITY IN THE YOUNG BEAGLE: SUBCELLULAR MORPHOLOGICAL CHANGES. J. E. Riviere,* E. J. Hinsman,* G. L. Coppoc,* W. W. Carlton,* J. A. Thornhill.* (Intr. by S. R. Ash) School of Veterinary Medicine, Purdue University, West Lafayette, Indiana 47907.

A single dose (15 mg/kg) of gentamicin (G) was administered intravenously to 4 purebred 5-month old beagles. Six 24-hour creatinine, urea, phosphate and osmolar clearances were performed, three before and three after G infusions, as were hematology and urinalysis. Animals were necropsied the fourth day after G infusion. As previously reported (Fed Proc 39:859, 1980), clearances decreased in treated animals. Light microscopy revealed no significant lesions. Electron microscopy demonstrated increased cytosomes with myeloid figures in the proximal tubules of treated dogs, a finding characteristic of G nephrotoxicity. Further examination of the proximal tubules revealed the presence of single membrane limited vesicles containing granular proteinaceous material in each G treated animal and not in the simultaneously run saline treated control. A structure of similar appearance has been reported in rats with osmotic nephrosis due to the administration of dextran, glucose, mannitol or sucrose. The significance and relationship of this structure to the pathogenesis of gentamicin nephrotoxicity is not known. Glomerular alterations were not seen.

THE PATHOGENESIS OF DRUG INDUCED PAPILLARY NECROSIS (PN): THE ROLE OF URINARY CONCENTRATION. S. Sabatini, K. Subbarayudu, N.A. Kurtzman, and J.A.L. Arruda, (intr. by Gordon Lang). Univ. of Illinois, Chicago, IL.

The pathophysiology of drug induced papillary necrosis is unknown. We studied this issue by administering 2 bromoethylamine (BEA) to rats. This drug when given intravenously produces papillary necrosis in 100% of animals. Four groups of animals were studied: 1) Heterozygous Brattleboro (BB), 2) Homozygous BB (central diabetes insipidus, DI), 3) Homozygous BB chronically injected with vasopressin and 4) Sprague Dawley rats receiving only 5% glucose as drinking fluid. One half of each group of animals was injected with BEA while the other half was sham injected. Uosm at the time of study 1723±37, 254±52, 1841±107, 299±46 mOsm/Kg H_2O in groups 1 to 4 respectively. The heterozygous BB rats developed all the functional and morphologic lesions of PN that we have previously described. Homozygous BB rats on the other hand, developed no manifestations of PN (i.e. animals with central diabetes insipidus were completely protected from the nephrotoxic effects of this drug). Administration of vasopressin to these animals fully restored the toxic effect of BEA. Lowering urinary concentration by glucose loading also fully protected against BEA induced PN. We conclude that the capacity to concentrate the urine is an essential prerequisite for the development of this drug induced form of PN. We speculate that the concentration of BEA in the papilla is necessary for this drug to exert its toxic effect. It is possible that manèuvers which lower urinary concentration may retard the development of PN in humans exposed to drugs that cause this syndrome.

IDENTIFICATION OF THE GENTAMICIN (G) RECEPTOR OF RENAL BRUSH BORDER MEMBRANES (BBM). M. Sastrasinh*, T.C. Knauss*, J.M. Weinberg, and H.D. Humes. University of Michigan, Ann Arbor, Michigan.

The initial event in the action of G on renal proximal tubular cells, its site of toxic action, occurs at the plasma membrane, and, as with other drugs and toxins, may be due to specific membrane receptors. To characterize this receptor, we examined the binding kinetics of ^{3}H-G to isolated BBM from rat kidney. G bound to BBM in a saturable, reversible fashion with a dissociation constant (K_d) of 6.39 μM, a maximal binding capacity of 2.10 nmoles/mg protein and a maximum binding concentration (B_{max}) of 1.77 μM. Scatchard analysis demonstrated that G bound to a single class of noninteracting binding sites. Treatment of BBM with trypsin had no effect on G binding, but exposure to phospholipase A or C decreased G binding by 40% and 20%, suggesting that the receptor is a phospholipid (PL). To assess G-PL binding, partitioning of G from water to chloroform in the presence of phosphatidic acid (PhA), phosphatidyl (Ph)-serine (PhS), Ph-inositol (PhI), PhI-4-phosphate (PhIP), PhI-4,5-diphosphate ($PhIP_2$), Ph-choline (PhC), and Ph-ethanolamine (PhE) was measured:

	PhA	PhS	PhI	PhIP	$PhIP_2$	PhC	PhE
K_d(μM)	6.73	6.03	11.42	3.44	7.49	no binding	
B_{max}(μM)	3.10	1.58	2.88	1.34	6.30		

G binding occurred only with acidic PLs with K_d nearly identical to BBM. These results identify the acidic PLs as the renal cell surface receptor for G and provide a basis to predict renal toxicity of other aminoglycosides by their affinity for the receptor, to identify competitive inhibitors which may ameliorate toxicity, and to better understand the initial toxin-membrane event which may be critical in developing nephrotoxicity.

RENAL VESSEL AND TUBULE PRESSURE AND FLOWS IN THE INITIAL PHASE OF CIS-DIAMMINE DICHLOROPLATINUM(Pt) NEPHROTOXICITY. R. SAFIRSTEIN: (intr. by S.Glabman) Mount Sinai School of Medicine, New York.

The earliest detectable fall in glomerular filtration rate (GFR) induced by Pt occurs, in rats, 48-72 hours after its administration (5mg/Kg). To determine the cause of the fall in GFR at this time whole kidney GFR and RBF (by PAH extraction), systemic pressure(AP) and protein concentration (C_A) were measured. Single nephron (SN)GFR as well as hydrostatic pressure in the proximal tubules(P_T) and glomeruli (P_{GC}) (estimated by stop-flow pressure (P_{SF}) and C_A) were measured in the same animals. To minimize the effect of extracellular fluid depletion consequent to surgical preparation for micropuncture, measurements were made in plasma replete animals. The results are: (mean±1SE; + $p<.05$ vs C)

	GFR	RBF	R_T	SNGFR	P_{SF}	P_T
	-ml/min-	mmHg/ml.min		nl/min	-mmHg-	
C	1.29±.1	8.2±.7	16±1	41±4	41±2	12±.2
Pt	.59±.1+	4.3±.8+	31±6+	27±1+	29±2+	10±.5+

Arterial pressure and protein concentration were unchanged from control. Thus total renal vascular resistance(R_T)was elevated. Lower transglomerular hydrostatic pressure difference was the result of diminished $P_{GC}$and not elevated P_T due to obstruction.

These experiments show that the earliest renal effects of Pt include an increase in total renal resistance, a decrease in total renal perfusion and a fall in glomerular hydrostatic pressure. It is therefore suggested that the early fall in filtration rate derives, at least in part, from hemodynamic changes including afferent arteriolar constriction.

TISSUE UPTAKE OF ATP IN ACUTE RENAL FAILURE. Norman J. Siegel, Irshad Chaudry,* Arthur E. Baue,* and Michael Kashgarian. Yale University School of Medicine, New Haven, Connecticut.

Previous studies have shown that the post-ischemic infusion of ATP-$MgCl_2$ accelerates the recovery of both glomerular and tubular function while the administration of ATP alone fails to have any beneficial effects. To determine the relationship between the tissue uptake of ATP and its salutory effects on recovery of renal function, rats were subjected to 45 minutes of renal ischemia and then infused with 25 μmoles of C^{14}-ATP either combined with $MgCl_2$ (25 μmoles) or alone. Thirty minutes later, samples of blood, liver and kidney were frozen in situ and cellular levels of ATP were determined after electrophoretic separation.

In sham operated animals, cellular levels of C^{14}-ATP in the kidneys were similar in rats which received ATP-$MgCl_2$ (0.90 ± 0.02 μmoles/gm) or ATP alone (0.81 ± 0.05). In animals with renal ischemia, the cellular levels of C^{14}-ATP in the kidneys were: significantly less than control values ($P < 0.01$) in rats given ATP alone (0.30 ± 0.02) but significantly greater than control values in animals treated with ATP-$MgCl_2$ (1.48 ± 0.15). In the ischemic animals, the cellular level of C^{14}-ATP was five fold higher in ATP-$MgCl_2$ treated animals as compared to rats given only ATP.

These data indicate that following an ischemic renal insult the cellular uptake of exogenous ATP by the kidney is augmented when combined with $MgCl_2$ and that this enhanced cellular uptake is correlated with an accelerated recovery of renal function.

PHOSPHOLIPID METABOLISM IN ACUTE TUBULAR NECROSIS (ATN). J.M. Slavicek* and C.H. Hsu. (Intro. by J. Lapides) Univ. of Michigan, Ann Arbor, Michigan.

Phospholipid metabolism during ATN induced by $HgCl_2$ was studied in rats during the early stages of injury. 24 h after $HgCl_2$ or NaCl injection, 4 h after ^{14}C-choline injection, a right uninephrectomy (RK) was performed to measure the initial incorporation into lipid (dpm/kidney) with the left remaining kidney (LK) measured at 48, 72, and 192h.

	24-RK	48h-LK	%+/-	Serum dpm/ml	Urine dpm/24h
NaCl (N=6)	98,269	129,490	+31.5	35,110	246,000
$HgCl_2$(N=6)	219,710	183,369	-13.5	48,570	801,500
p value	<.005	<.002	<.001	<.005	<.001
	24h-RK	72h-LK			dpm/48h
NaCl (N=5)	87,174	120,318	+41.6	30,403	569,295
$HgCl_2$(N=6)	264,170	150,551	-39.5	30,864	1,110,318
p value	<.01	NS	<.001	NS	<.005
	24h-RK	192-LK			dpm/168h
NaCl (N=5)	141,629	72,614	-48.9	15,820	1,025,863
$HgCl_2$(N=6)	390,257	90,078	-76.1	13,748	1,655,223
p value	<.001	NS	<.001	NS	<.003

In another group of rats injected with [^{14}C]-choline 68 h after $HgCl_2$ or NaCl treatment the results were:

	72-RK	96h-LK	%+/-	Serum dpm/ml	Urine dpm/24h
NaCl (N=6)	89,908	117,337	+31.6	39,238	182,022
$HgCl_2$(N=6)	129,299	168,160	+33.1	46,580	490,138
p value	<.02	<.005	NS	NS	<.008

TLC analysis showed that the gain or loss of dpm/kidney were predominantly due to a gain or loss of phosphatidylcholine (PC). The results demonstrate that in the early stages of ATN an increased rate of PC synthesis was associated with an increased rate of degradation, however, by 72 hours after insult net synthesis of PC for membrane formation had occurred.

● PODOCYTE CHANGES IN EARLY ACUTE RENAL FAILURE (ARF) K. Solez, C.D. Malis*, W. Franklin*, L.C. Racusen*, and A. Whelton, Johns Hopkins Hosp., Baltimore, Md.

Renal ischemia may reduce K_f but has also been reported to increase glomerular permeability to serum proteins, an effect which would promote cast formation by causing precipitation of protein in tubular fluid. Podocyte abnormalities (PA) seen by scanning EM in ARF may reflect either of these changes in glomerular function. We found PA (flattening of cell bodies with apparent lack of foot processes) early in ARF caused by 1 hr of pedicle clamping in rabbits, a model in which tubular obstruction by casts and mild proteinuria occur. Increased glomerular permeability to ferritin was found. PA 1-2 hrs after unclamping were significantly lessened by two agents which are reported to prevent ARF and cast formation in this model: clonidine (30μg/kg i.v. bolus ½ hr before unclamping) and 5% mannitol (5% body weight infused 1 hr before clamping). PA were greater 1 hr after unclamping than they were 48 hrs after. No PA were observed in aminoglycoside-induced ARF (tobramycin 75 mg/kg/day x 14 days) in which decreased K_f occurs. PA were observed in 1 hr post-transplant biopsies from 9 patients who later developed clinical "ATN" (serum Cr≥2.5 mg/dl on day 3) and were significantly less severe in 6 patients with good post-transplant function (Cr<2.5 mg/dl on day 3). PA assessed by morphometry in these biopsies correlated with Cr on day 3 ($r=.86$, $p<.01$). We conclude that PA occur early in clinical and experimental post-ischemic ARF, are greater in those groups which eventually develop more severe ARF, and probably reflect increased glomerular permeability to protein leading to increased cast formation, rather than decreased K_f.

● STUDIES ON THE PATHOGENESIS OF RENAL FAILURE IN A RAT MODEL OF MULTIPLE MYELOMA. P. Smolens,* H. J. Reineck, M. Venkatachalam, and J. H. Stein, (intr. by R. Gibney). Univ. of TX Hlth. Sci. Ctr., Depts. of Med. and Path., San Antonio, TX.

Renal failure is a serious and frequent complication of multiple myeloma. Histologically, the typical "myeloma kidney" is characterized by distal tubular cast formation. It has been proposed that the specific Bence Jones protein (BJP) which is produced by a myeloma tumor may play an important role in the genesis of this cast nephropathy and that BJP with relatively high isoelectric points (pI) are nephrotoxic.

We have utilized a rat model of multiple myeloma to further evaluate the relationship between Bence Jones proteinuria and the development of renal failure. Animals with spontaneously occurring immunoglobulin secreting tumors were kindly provided by Dr. H. Bazin (Louvain, Belgium). Tumors from these animals were transplanted to an homologous strain of rats. Three different tumors have been studied, each secreting a distinct BJP as characterized by cellulose acetate electrophoresis, immunoelectrophoresis and pI determination. All rats excreted BJP within one to two weeks after transplantation and were maintained on a diet designed to produce an acid urine and maximal urinary concentration. Initial Uosm exceeded 2500 and urine pH was 5.5 to 6.2. Rats excreting BJP of pI 8.2 (N=5) and 6.7 (N=12) for periods of up to 40 days had virtually normal renal histology and serum creatinine concentrations (S_{Cr}) similar to those of control animals on the same diet. Rats excreting BJP of pI 5.2 (N=4), however, were found to develop cast nephropathy within 2 weeks of transplantation and S_{Cr} was increased two fold. These findings suggest that in this model, BJP of high pI are not necessarily more nephrotoxic than BJP of low pI and that factors other than pI must be important in the genesis of the lesion of the myeloma kidney.

EFFECT OF POTASSIUM DEPLETION ON CARDIAC SYMPATHETIC ACTIVITY. Kate Spokes*, James Young*, and Franklin H. Epstein. Charles A. Dana Research Institute and Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, Mass.

Potassium depletion is associated with a reduction in blood pressure and impaired responsiveness to vasopressors and pressor reflexes. Peripheral sympathetic activity was therefore studied in potassium-depleted rats by measuring the turnover of norepinephrine in cardiac muscle. Twenty-five female Sprague-Dawley rats weighing 150 to 200 g were placed on a potassium-deficient diet for 14 days and compared with pair-fed controls. Serum potassium averaged 2.1±0.08 mEq/L in K-depleted rats compared with 3.6±0.11 in controls. Skeletal muscle potassium fell to 275±10 mEq/g dry solids from 359±15, a drop of 24%, $p < 0.01$. Potassium contents of heart and liver, however, were not significantly reduced. Peripheral sympathetic activity was assessed by measuring the specific activity of norepinephrine in cardiac muscle 2, 6, 12 and 24 hours after injecting a tracer dose of ^{3}H l-norepinephrine to label tissue stores. The turnover of cardiac norepinephrine was unchanged by K depletion (half-time 12.7 hrs in control; 13.4 in depleted rats). Sympathetic nervous activity in heart muscle of rats thus appears to be unaffected by moderate potassium depletion.

SERUM VANADIUM (V) CONCENTRATION IN CHRONIC RENAL FAILURE(CRF). SM Sprague*, A Fregene*, B Wilkinson* J Costantino, RW Rosenbaum, and GH Mayor, Michigan State University, East Lansing, MI.

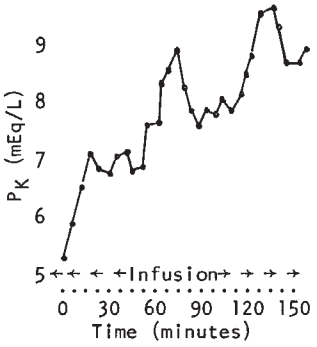
Because V has been shown to: 1)be a potent inhibitor of NA^+-K^+ATPase, 2) effect a naturesis in rats 3) increase in the serum of nondialyzed uremic subjects; it has been suggested that these increased serum concentrations may in part account for the increased FE_{Na} seen in uremia. This study was initiated to determine if serum V concentrations increase with CRF and can therefore be involved in the adaptation to uremia. Serum V concentrations were determined by neutron activation analysis in normal control subjects, nondialyzed patients with stable CRF, and CRF patients on hemodialysis (HD). This method has a detection limit of 2ng/ml and a precision of ±5%.

	Age	Creatinine mg/dl	Vanadium ng/ml
Control(n=110)	49.2±23.3	1.3±0.38	25.5±44.7
CRF(n=9)	53.2±21.0	8.1±2.60	18.1±28.0
HD(n=21)	49.3±15.5	--------	16.6±41.8

There were no significant differences in the age or sex of any group. Serum V concentration ranged from undetectable to 190 ng/ml in controls, undetectable to 89 ng/ml in CRF patients and undetectable to 190 ng/ml in HD patients. Analysis of variance revealed no significant differences between the three groups with respect to serum V concentration. Linear regression analysis did not demonstrate a relationship between creatinine and V. In addition, V did not change with age within the control group. These data suggest that serum V concentrations are independent of renal function and age and, thus, probably do not play a role in the adaptation to uremia.

PERIODIC RAPID CELLULAR K^+ UPTAKE (CKU) DURING K^+ INFUSION IN AWAKE ANEPHRIC DOGS. R.H. Sterns, M. Hyk*, R. Melly*. U.Roch.Sch.Med., Rochester, NY.

In renal failure, CKU is the dominant defense against hyperkalemia. To study this, P_K was measured q. 3-10 min during K^+ infusion (inf) (0.8 mEq/kg/hr for 2.5 hrs) in nephrectomized (Nx) dogs. In 5 dogs studied 1 hr post Nx during pentobarbitol anesthesia, P_K rose at a constant rate. In contrast, in 6 awake dogs studied 18 hrs post Nx, periods of limited CKU alternated with periods of rapid CKU during which, despite continuing K^+ inf, P_K either failed to rise or fell by up to 1.5 mEq/L. Plasma insulin (I) oscillated during inf varying between basal and 4-5x basal levels in parallel with P_K ($p < .001$). However, these changes in [I] were not causally related to the changes in CKU since similar periods of rapid CKU were observed in 3 awake pancreatectomized (Px) dogs inf with K^+ and a constant replacement dose of I (fig). The net increase in P_K during inf was similar in Px and non-Px dogs (3.2 ± .2 vs 3.2 ± .4 mEq/L). The fig illustrates a study in an awake Nx, Px dog inf with I (6 mU/kg/hr) + K^+ (0.8 mEq/kg/hr).



Conclusion: K^+ inf in conscious Nx dogs induces periods of rapid CKU which are associated with but not caused by K^+-induced I secretion, and serve as an important defense against hyperkalemia.

PROSTAGLANDIN SYNTHESIS BY GLOMERULI ISOLATED FROM RATS WITH GLYCEROL-INDUCED ACUTE RENAL FAILURE. J. Sraer, J.D. Sraer, L. Moulonguet, W. Siess and R. Ardaillou (intr. by C. Lechene) Hôpital Tenon and Institut Pasteur, Paris, France.

In vitro PG synthesis by glomeruli isolated from rats with glycerol-induced (30 mmoles/kg, i.m) acute renal failure (ARF) was measured by radiometric high performance liquid chromatography. The same PGs (6 keto $PGF_{1\alpha}$, TXB_2, $PGF_{2\alpha}$ and PGE_2) were synthesized by glomeruli from control and treated rats sacrificed 1 and 24 hr. after glycerol injection, but their synthetic rates were clearly different. At 24 hr., all PGs were produced in a greater amount by the glomeruli from treated rats whereas at 1 hr. the only change was a decrease in PGE_2 synthesis. Thus, we studied PGE_2 synthesis by glomeruli at various times after induction of ARF, using RIA. PGE_2 synthesis with and without arachidonic acid was lower at an early period (1 hr) and greater at a late period (28, 48 and 72 hr) of ARF than in the control preparations. There was no difference at the beginning (0.5 hr), during an intermediary stage (2 and 4 hr) and at the end of the period tested (192 hr). The synthetic rates of $PGF_{2\alpha}$ and TXB_2 also measured by RIA were identical initially (1 hr) and greater later on (24 hr). The late increase in PGE_2 synthesis could be attributed to stimulation of the renin-angiotensin system since it was suppressed in rats treated for 48 hr. before glycerol administration by captopril. The early decrease in PGE_2 synthesis appeared as specific for the glomeruli since it was not observed with papillary homogenates. These data demonstrate that only PGE_2 and only from glomerular origin is produced at a lesser rate at an early stage of glycerol-induced ARF. This suggests a role for this event in the mechanism of ARF.

● A NEW MODEL FOR STUDYING DRUG-INDUCED NEPHROTOXICITY: THE RAT WITH UNTREATED STREPTOZOTOCIN-INDUCED DIABETES MELLITUS (DM). C.A. Vaamonde, R.B. Teixeira*, J. Morales*, J. Kelley*, H. Alpert*, & V. Pardo. Dept. of Medicine & Pathology, Univ. of Miami and VA Medical Center, Miami, FL.

Because high renal solute excretion protects against nephrotoxic acute renal failure (ARF), we studied the effects of the spontaneous, stable, high solute diuretic state of female Sprague-Dawley rats with DM on the nephrotoxicity of gentamicin (G), 40,70 & 200 mg/Kg/d for 11-14 d; and cisplatinum (Pt), 6 mg/Kg single dose. Controls (C) were age-matched rats identically treated. DM rats had diabetes for 4-6 mos and all were hyperglycemic (>500 mg/dl) and glycosuric (8-12 g/d) at study time. Animals were kept in individual metabolic cages for 1 (Pt) or 3 (G) wks.

G and Pt caused ARF in all C rats: max Δ in Ccr were ↓ 85±6% with G-40 ($p<.001$) and ↓ 87±7% with Pt ($p<.001$). All C rats developed severe acute tubular necrosis (ATN). In marked contrast, DM animals showed no ↓ in GFR (G-40, ↑ 33±5%, $p<.001$ vs. C; G-70, ↑ 25±8%, $p<.001$ vs. C; Pt ↑ 22±11%, $p<.001$ vs. C) and no histologic evidence of ATN. All DM rats survived G-200 for 11 days, while no C rat survived beyond day 6. In rats with diabetes of short duration (5 wks) similar protection was found with G-40: max Δ Ccr: C, ↓ 72±9%, DM ↑ 20±9%; $p<.001$. DM rats that spontaneously lost their hyperglycemia, glycosuria and polyuria became sensitive to G-40.

We conclude that the high solute diuresis in DM rats affords complete protection against various nephrotoxins and that the DM rat is a useful model to study the induction and preventive mechanisms of drug-induced nephrotoxicity.

● FUNCTION OF GLOMERULAR POLYANION (GPA). V. Matti Vehaskari,* Frederick G. Germuth, Jr., and Alan M. Robson. Dept. Peds., Wash. Univ., St. Louis, MO.

To determine the functional role of GPA, glomerular charge was neutralized by a pulse infusion of either protamine sulfate (PS), hexadimethrine, or poly-l-lysine into one renal artery of normal Sprague-Dawley rats. Contralateral kidneys were infused with the vehicle solution as paired controls. Urines were then collected from each kidney for up to 10 h with the animals awake.

Each polycation induced a statistically significant, unilateral increase in proteinuria due to a selective increase in albuminuria. The effect, maximal in the first hour, was dose dependent as shown for PS:

Albuminuria (experimental/control kidney) - mg/h

Dose,mg	1st h	2nd h	3rd h
0.5	1.46/0.27**	0.85/0.34**	0.58/0.36
0.75	2.22/0.44**	1.68/0.41**	1.08/0.35
1.0	2.90/0.29**	2.34/0.31**	1.92/0.33*

* = P<0.05, ** = P<0.01

Differences in albuminuria were even greater when factored by either GFR or RPF. Absolute excretion of non-albumin protein was identical in experimental and control kidneys representing 6.2 and 48.8%, respectively, of total protein. Albuminuria returned to control levels 4 h after infusion of 0.5 mg PS, later with higher doses. Renal morphology at the height of albuminuria showed only patchy foot process fusion with decreased staining for GPA. We conclude that polycation infusion temporarily increases permeability of glomerular capillary membranes to anionic molecules (e.g., albumin) independently of hemodynamic changes or systemic factors, presumably by selective neutralization of the charge-barrier.

● MITOCHONDRIAL DYSFUNCTION IN MERCURIC CHLORIDE (Hg) NEPHROTOXICITY. J.M. Weinberg, P.G. Harding*, and H.D. Humes. University of Michigan, Ann Arbor, MI.

Accumulating evidence implicates altered bioenergetics as an important contributing factor to compromised renal tubular cell function and integrity in the developing phases of nephrotoxic and ischemic ATN. The literature, based largely on relatively insensitive histochemical methods, is unclear, however, on whether damage to renal cortical mitochondria (M) precedes advanced cell injury produced by the extensively studied nephrotoxin, Hg. Though Hg may act at several cell sites to injure renal tubular epithelium, M show high sensitivity. In vitro exposure of M to 10 or 100 µg/ml Hg produced transient respiratory stimulation followed by complete inhibition of State 3 (S3) and DNP uncoupled (DNP) respiration 1 µg/ml Hg produced sustained respiratory stimulation. As assessed by M swelling techniques, all 3 concentrations of Hg increased permeability of M to K^+ and Na^+. 100 µg/ml Hg blocked PO_4 transport by M. To assess in vivo activity, groups of 6-8 rats received 4 mg/kg Hg s.c.(E) or sham solution (C). Compared to C, at 2 hours, a time prior to major morphological changes, renal cortical M from E showed decreases in S3 respiration (↓14% $p < .001$), DNP respiration (↓11% $p < .001$) and ADP translocase activity (↓28% $p < .001$). At 3 hours M ATPase activity was also inhibited (↓22% $p < .01$). M permeability to Na^+ and K^+ was increased in E but M phosphate transport was not affected. These data demonstrate that alterations in M occur during the earliest phases of renal tubular injury by Hg. Because of its previously well defined course of action at the whole organ level, Hg will be of value in critically assessing the role of toxin-M interactions in nephrotoxicity.

INCREASED MUSCLE DEGRADATION AND 3-METHYLHISTIDINE RELEASE IN FASTED, UREMIC RATS. Steven J. Wassner, and Jeanne B. Li.* Penn State University, M.S. Hershey Med. Ctr., Hershey, Pa.

Uremia is associated with abnormalities of protein metabolism most evident as decreased growth and diminished muscle mass. Muscle protein degradation was assessed by determining 3-methylhistidine (3MH) release from myofibrillar protein in uremic (U) (SUN 63.5 ± 4.3 mg/dl, x̄ ± SE) and sham-operated (S) (15.9 ± 1.1 mg/dl) rats in the fed state and after 24 and 48 hr of fasting. 3MH is a component of actin and myosin that is released from muscle tissue during myofibrillar degradation. Both groups were growing but body weight (BW) was significantly less in U rats. After 48 hr of fasting, U lost a greater percentage of BW (17.1 vs 13.2%). Muscle atrophy paralleled weight loss. Urine and plasma 3MH levels were measured in all groups and muscle 3MH levels were measured in fed and 48 hr fasted rats. In the fed state, U rats had higher plasma and muscle 3MH levels and excreted 17% more 3MH than S rats (0.9 vs 0.77µmol/100 gm BW/24 hr). With fasting, plasma 3MH levels increased and at 48 hr, urinary 3MH excretion rose to 1.42µmol/100 gm/24 hr. Muscle 3MH content increased in both U and S rats (S,2.0 - 4.7 and U, 6.4 - 28.9 nmol/gm tissue). Calculation of muscle degradation, based on the change in total body 3MH pool, revealed that U degraded a greater percentage of muscle than S rats (15.7 vs 11.8%) during a 48 hr fast. Uremia is associated with increased myofibrillar breakdown during moderate stress. This increased muscle degradation rate in uremia would not be apparent if only urinary 3MH excretion was measured. (Supported by Muscular Dystrophy Association and NIH (AM24061)).

ACUTE RENAL FAILURE AFTER ANGIOGRAPHY: PROSPECTIVE STUDY. L. Weinrauch,* M. Alday,* M. Clouse,* C. Malarick,* K. Unger,* R. Gleason,* A. Kaldany, and J. D'Elia. Joslin Clinic Renal Unit, N.E. Deaconess Hospital and Harvard Medical School, Boston, Mass.

Three hundred seventy-eight patients undergoing non-renal angiograms were followed for acute renal failure (ARF). A point score was totaled:

Rise in serum creatinine	≥ 1.0 mg%	6 points
	0.5-0.9 mg%	4
24 hour persistent nephrogram		2
pyeloureterogram		1
24 urine volume	< 300 cc	2
	300-500 cc	1
urine sediment ARF index	severe	2
	moderate	1 point

Group A. Definite ARF (≥ 6 points), Group B. Probable ARF (4-5 points), Group C. Possible ARF (2-3 points), Group D. No ARF (0-1 points).

Background Data Groups	A (n=16)	B (n=3)	C (n=22)	D (n=337)
Azotemia (BUN/creat ≥ 30/1.5 mg%)	69%	33%	23%	5%
Proteinuria (≥ 50 mg%)	50	33	0	9
Anemia (Hemoglobin. ≤12 gm%)	56	67	32	17
Diuretic	56	67	32	41
Diabetes	63	33	41	33

Two Group A patients required K+ exchange resin, three required acute dialysis. No patient required maintenance dialysis or died from ARF. Whereas nonazotemics had a 2-7% incidence of definite-possible ARF, azotemic patients (mean BUN/creat = 47/2.3 mg%) had a 33-55% risk. In the absence of chronic azotemia, diabetes represented no added risk.

EFFECT OF PARATHYROID HORMONE (PTH) REDUCTION BY CIMETIDINE ON THE GLUCOSE INTOLERANCE OF UREMIA. José R. Weisinger, Carlos Perez-Schael,* Eduardo Coll-García,* Pablo Amair,* Luis Gutierrez,* Douglas Urbina,*,Valentina Wallis,* and Virgilio Paz-Martinez. Departments of Medicine and Physiology, Dialysis Unit. Clinical Research Laboratory. Universidad Central de Venezuela. Caracas.

Cimetidine (C) a histamine H_2- receptor antagonist, has been shown to be effective in therapeutic doses in supressing the high levels of immunoreactive PTH of chronic uremia, without affecting the serum concentration of calcium, phosphorus or magnesium. At the same time PTH has been proposed as one of the toxic factors and a possible cause of the glucose intolerance of uremia.

To further delineate this effect, we performed oral glucose tolerance tests in chronically hemodialyzed patients before and after one month of oral cimetidine (800 mg daily).

The results showed a decrease in the levels of immunoreactive PTH using a radioimmunoassay with an antibody highly specific for the carboxyl terminal fragment, with values of 248 ± 52.1 and 108 ± 27.3 µl-eq per mililiter, before and after C respectively ($p < 0.01$).

The glucose response determined by the area under the glucose curve (Mean Weight response) showed an important improvement with values of 23.1 ± 0.4 and 20.8 ± 0.6 gm/ min, before and after C ($p < 0.01$).

The insulin response did not show any significant change after C therapy.

We conclude that the Cimetidine induced PTH reduction produces an improvement of the carbohydrate intolerance of uremia, probably due to the decrease of circulating PTH levels.

● LOSS OF THE GLOMERULAR CONTRACTILE RESPONSE TO ANGIOTENSIN IN RATS PROTECTED AGAINST ACUTE RENAL FAILURE BY PRIOR INSULT. B.M.Wilkes* and N.K. Hollenberg, Peter Bent Brigham Hosp, Depts. of Med. & Radiol., Boston, MA.

We measured the contractile responses of glomeruli isolated by sieving techniques to angiotensin II (AII) and dibutyryl cyclic AMP (DBcAMP). In healthy rats AII (10^{-4} g/L) reduced mean glomerular diam.(control, 156.6±1.0 µm AII, 112.8 ±1.1 µm; p<.001). Similarly, DBcAMP(10^{-4}g/L) reduced the size of normal glomeruli (156.6±1.0 vs 119.4± 1.0 µm; p<.001). Saralasin (PII3)(10^{-4}g/L)had a small but significant agonist effect;when superimposed on AII, PII3 totally blocked the glomerular response. The reduction in glomerular size with DBcAMP was partially blocked by PII3. Two wks following ARF induced with 50% glycerol (10ml/kg,i.m.)we confirmed that the response to $HgCl_2$ (4.7 mg/kg,s.c.)was blunted (p<.001). AII was totally ineffective in reducing glomerular size (control, 144.8±1.5 um;AII 142.2±1.5 µm), but there was a substantial response to DBcAMP(144.8±1.5 vs 131.8±1.6 µm;p<.001). To determine the specificity of the loss of the glomerular response to AII 2 wks after glycerol, the effects of an AII infusion (1 µg/kg/min) on blood pressure (BP) and renal blood flow (RBF) were assessed. There was a substantial rise in BP (control, 104±11.8 mmHg; AII 131.0±5.3 mmHg;p<.001) and fall in RBF (control, 2.45±0.52 vs AII, 0.81±0.10 ml g^{-1}min $^{-1}$;p<.025). Vascular responsiveness to AII was preserved at a time when glomeruli were totally unresponsive and rats were resistant to ARF. The loss of glomerular contractility may, in part, account for the protection from ARF seen in this model, inferring that glomerular abnormalities play a role in pathogenesis.

DISSOCIATION BETWEEN PROXIMAL TUBULAR CELL DYSFUNCTION AND ACUTE FALL IN GLOMERULAR FILTRATION RATE (GFR): STUDIES IN GLYCEROL INDUCED ACUTE RENAL FAILURE (ARF). C. Westenfelder, P.A. Crawford, R.K. Hamburger, R.L. Baranowski, and N.A. Kurtzman. Univ. of Illinois, Chicago, Illinois.

It has been suggested that the acute fall in GFR in ARF is mediated by a tubulo-glomerular feedback mechanism (Thurau et al). According to this hypothesis increased distal salt delivery (2^{o} to depressed proximal reabsorption) causes a fall in GFR via a macula densa mediated rise in angiotensin II production by the juxtaglomerular apparatus. To test the applicability of this hypothesis in conditions which have been reported to afford protection against ARF, we examined GFR (^{125}I-iothalamate clearance) and proximal tubular function (glucose and HCO_3 reabsorption) in 51 saline loaded (SL, 1% NaCl for 5 wks) and 38 glycerol rechallenged (RC, reinjection of glycerol after recovery from a prior episode of ARF) rats, when measured 24 hours after glycerol (50%, 10 ml/kg i.m.). GFR fell by 60% in both groups. HCO_3 and glucose reabsorption was markedly depressed in SL and entirely normal in RC animals. Distal acidification and K secretion were intact in SL and RC rats. These data demonstrate, that 1) neither SL nor a prior episode of ARF prevents ARF and 2) that the fall in GFR can be associated (SL) or dissociated (RC) from proximal tubular dysfunction. Conclusion: these observations fail to support the notion that the fall in GFR in this model of ARF is mediated by a decrease in proximal tubular reabsorption.

SALINE DRINKING AFTER GLYCEROL (G) PROTECTS AGAINST ACUTE RENAL FAILURE. B.M.Wilkes* and N.K.Hollenberg. Peter Bent Brigham Hosp.,Depts. of Med. & Radiol., Boston, MA.

To determine if chronic saline ingestion was required for protection from acute renal failure (ARF), the effects of acute and chronic ingestion of 1% saline were studied in rats injected with 50% G (v/v,10 ml/kg,i.m.). The standard group (WW) drank tap water throughout. One group (SS) drank saline for 1 month prior to and following insult.A third group (SW) was given saline only after insult. At24h severe ARF developed in the WW group (BUN 114.5±6.1 mg/dl). SS rats demonstrated striking protection (BUN 49.0±4.0 mg/dl). Equivalent protection occurred when saline was offered only after insult (WS, BUN:57.4 ±5.8 mg/dl). When saline was replaced by water following G (SW), all protection was lost (BUN, 109.6±8.2 mg/dl). "Pre-renal" factors were compared in all rats offered either saline or water post-insult. Fluid intake fell to 1/3 normal in the water group (normal, 30.2±1.3 vs.water 8.5±1.0 ml/100g BW/24h, p<.001) but was preserved in the saline group (32.3±3.0). Plasma volume was preserved (saline, 4.38±0.30 vs. water, 2.75±0.22 ml/100g BW, p<.001). There was a significant negative correlation between the BUN and plasma volume (r= -0.601, p<.001). There was a small reduction in mean arterial pressure (MAP)(93.5±4.0 mmHg) in the water group, but MAP was not different from normal (102.8±3.0 mmHg) in the saline group (97.5±4.0 mmHg). We conclude that saline drinking prevents azotemia only when ingested post-insult and acts, at least in part, by reversing pre-renal factors.

ADRENAL ANDROGENS (AA) IN END STAGE RENAL DISEASE (ESRD). RL Winer, M Rajudin*, LN Parker*, WR Skowsky*. Dept. of Medicine, VA Medical Center, Long Beach, and University of California, Irvine.

A variety of endocrine abnormalities, including gonadal dysfunction, have been described in ESRD. In view of gonad-adrenal similarities with respect to androgen synthetic pathways, we measured AA response (androstenedione:Δ^4-A; dehydroepiandrosterone:DHA; dehydroepiandrosterone sulfate:DHAS), as well as cortisol (F) and aldosterone (aldo), to a 4-hour infusion of α1-24 corticotropin. Ten patients (9 male) with ESRD (4 hemodialysis, 6 C_{cr} <10 ml/min) and ten hospital controls (C_{cr}>85 ml/min) were studied. Results are given as mean ± SEM.

	Baseline		4 hours	
	Control	ESRD	Control	ESRD
Δ^4-A(ng/ml)	1.2±0.5	1.2±0.2	2.4±0.8	2.2±0.3
DHA (ng/ml)	2.6±0.5	2.1±0.3	7.1±1.0	7.3±1.0
DHAS(µg/dl)	79 ± 16	116± 14	100± 19	140± 15
F (µg/dl)	13.1±1.9	17.6±1.5	37.4±2.2	47.9±1.8
Aldo(ng/dl)	13.5±1.4	16.7±1.8	21.2±1.6	39.8±3.9

All 3 AA increased following corticotropin infusion ($p<.001$), and there was no difference in basal values or response between the groups. There was no difference in basal F or aldo and both groups responded to stimulation ($p<.001$), but the increase was greater in ESRD ($p<.05$). The augmented F response may, in part, reflect decreased clearance in ESRD. Under the conditions of this study, the results suggest that patients with ESRD have no abnormality in production of AA, in contrast with previously noted Leydig cell deficiency. Furthermore, overall adrenal steroidogenesis of glucocorticoids, mineralocorticoids, and androgens appears to be intact in ESRD.

GLUCOCORTICOID (GC) ENHANCEMENT OF PHYSIOLOGIC PROTEINURIA, R. A. Zager, Ohio State University Hospital, Columbus, Ohio

Pharmacologic doses of GC increases urinary protein excretion in normal animals and in some patients with renal disease. The mechanism of this effect is unknown. However, GC increases GFR and GC is also required for the induction of renin/angiotensin (R/A) proteinuria. Therefore, the present studies were done to determine whether changes in GFR or the R/A system mediate the GC-proteinuric response. Urinary albumin and lysozyme (as markers of glomerular permeability and tubular protein reabsorption respectively) and GFR (Cioth-I^{125}) were measured in sodium loaded and depleted rats subjected either to acute GC treatment (2 mg/kg dexamethasone) or to acute volume expansion with rat serum to abruptly raise GFR. We found that: (1) GC produced an immediate increase in GFR and albumin and lysozyme excretion rates (mean +45%,+20%, +55% respectively). ($P < 0.05$, all cases.) (2) The acute albuminuric response to GC was not quantitatively different from that observed in rats whose GFR was similarly increased by normal rat serum infusions. (3) A late and quantitatively greater (4-40X basal values) albuminuric response occurred 14-32 hours post GC administration, a time at which GFR and lysozyme excretion rates were normal. (4) This late albuminuric phase was independent of dietary sodium intake and could not be reproduced acutely by infusion of serum harvested from GC pretreated albuminuric rats.

Conclusion: GC produces a biphasic proteinuric response: an early phase which is largely GFR dependent and a late albuminuric phase which may be due to GC-induced enhancement of glomerular permeability to macromolecules.

INTRINSIC, PTH-INDEPENDENT PHOSPHATE (P) TRANSPORT IN THE ISOLATED UREMIC PROXIMAL TUBULE. Norimoto Yanagawa* and Leon G. Fine. Division of Nephrology, Center for the Health Sciences, UCLA School of Medicine, Los Angeles, California.

Adaptation of tubular phosphate transport (J_P) associated with a reduction in renal mass may be due to intrinsic alterations in tubular cell function or may be mediated by humoral factors such as PTH. The present study examined J_P in rabbit proximal straight tubules (PST) from normal (N), hyperparathyroid-uremic (U-HP), and euparathyroid-uremic (U-NP) rabbits. Fractional P excretion (FE_P) was < 4% in N and U-NP and > 13% in U-HP. The existence of biologically significant hyperparathyroidism in U-HP was confirmed by demonstrating inhibition of J_P in normal PSTs by U-HP sera only. PSTs from all three groups were perfused in vitro in a bath of normal rabbit serum and J_P lumen-to-bath (lb), J_P bath-to-lumen (bl), and net fluid reabsorption (J_V) were measured.

	J_P (lb)	J_P (bl)	J_P (net)	J_V
N	5.17±1.02	0.80±0.18	4.37±0.50	0.43±0.06
U-HP	7.66±1.35	2.13±0.54	5.56±1.20	0.96±0.19
U-NP	10.51±0.96	2.42±0.94	7.58±0.79	0.68±0.18

Conclusions: 1. Reduction of renal mass leads to an increase in J_P (lb) in the PST. 2. This adaptation may be related to the requirement to reclaim more filtered P since SNGFR is increased in this model. 3. For the same decrease in GFR, J_P (lb) is lower in U-HP than U-NP, reflecting the greater in vivo FE_P of U-HP rabbits. 4. The adaptation may be induced by parathyroid status in vivo, but is expressed in vitro independently of PTH concentration and the rate of fluid reabsorption.

● PROSTAGLANDINS (PG) AND RENAL FUNCTION IN CHRONIC BILE DUCT LIGATED-CIRRHOTIC DOGS. Edward J. Zambraski and Michael J. Dunn. Dept. of Physiology, Rutgers Univ., New Brunswick, N.J. and Dept. of Medicine, Case Western Reserve Univ., Cleveland, OH.

To evaluate the role of PG in determining kidney function and renal hemodynamics in cirrhosis, the common bile duct was ligated (CBDL) in 15 dogs. CBDL for 4-12 weeks increased mean serum bilirubin from .14 to 3.83 mg/dl and alkaline phosphatase from 97 to 1903 IU. PGE_2 excretion rates before and after chronic CBDL were 1.9±.2 and 3.4±.7 ng/min. Under pentobarbitol anesthesia mean arterial pressure (MAP) (mmHg), left kidney blood flow (RBF) (ml/min) and distribution, glomerular filtration rate (GFR) (ml/min), sodium excretion (UnaV) (µeq/min), urine sodium (Una) (meq/l) and PGE_2 excretion (PGE_2-U) (ng/min) were measured before and after indomethacin (INDO), (2mg/kg i.v.). Values are mean ± SEM. (+ $P < .05$, paired T test).

	No Ascites (N=8)		Ascites (n=7)	
	Pre-INDO	Post-INDO	Pre-INDO	Post-INDO
MAP	109±8	117±9+	92±10	108±13+
RBF	206±33	144±25+	229±19	148±22+
GFR	15±3	11±3+	22±3	13±3+
UnaV	16±6	17±6	21±11	13±7
Una	120±23	112±26	95±33	79±38+
PGE_2-U	3.2±.4	.3±.1+	2.8±.5	.5±.1+

RBF was redistributed to the outer cortex by INDO. INDO did not reduce RBF or GFR in 4 sham-operated dogs despite 90% reduction in PGE_2-U.

These data demonstrate that PG are important for the maintenance of renal hemodynamics in cirrhosis with or without ascites. Under these conditions drugs which inhibit PG synthesis may have a deleterious effect on renal function.

RED CELL DEFORMABILITY IN UREMIA. Nicholas Zerefos, Electra Xefteri, Charalambos Stathakis, Costantin Sombolos and George Daikos. University of Athens, 1st Department of Propedeutic Medicine, Greece.

Red blood cell deformability (R.B.C.d) was measured by means of a filtration technique in 18 healthy individuals (group A),16 non dialyzed uremics (group B) and 24 regular chronic hemodialyzed (C.H.D) patients (group C). The blood was filtered through a "Nucleopore" polycarbonate sieve containing cylindrical channels 5 μm in diameter. Results were expressed as the volume of R.B.C.s ($V_{R.B.C}$), filtered per minute. $V_{R.B.C}$ values of groups A, B and C were respectively 0,42 (S.D. 0.09), 0,35 (S.D. 0.007) and 0,38 (S.D. 0.10). Paired t-test evaluation showed a significant difference between healthy individuals and uremic patients (t 2.43, p 0.05), while no significant differences were observed between groups A and C. The above data suggest that: a) R.B.C.d. is impaired in uremia and b) the above abnormality is corrected by C.H.D.

● STIMULATION BY OXYGEN FREE RADICALS OF PROSTAGLANDIN PRODUCTION BY ISOLATED RAT GLOMERULI. R. Ardaillou, L. Baud, and M.P. Nivez (intr. by T. Dousa) Hôpital Tenon, Paris, France.

Polymorphonuclear leukocytes secreting free oxygen radicals are found in the glomerular capillaries at an early stage of experimental acute glomerulonephritis. The aim of this work was to study the effects of these radicals on prostaglandin (PG) production by the glomeruli. Glomeruli were isolated from rat renal cortex and incubated with a biochemical system capable of generating free oxygen radicals (addition to 100 μM xanthine of increasing concentrations of xanthine-oxidase). Synthesis of PGE_2, $PGF_{2\alpha}$, 6 keto $PGF_{1\alpha}$ and TXB_2, estimated using RIA, was twofold greater in the presence of oxygen free radicals. This effect was inhibited by catalase, slightly stimulated by superoxide dismutase and unaffected by hydroxyl radical scavengers thus demonstrating that hydrogen peroxide (H_2O_2) was the by-product responsible. This was confirmed by the stimulatory effect of H_2O_2 itself since PG production progressively increased to reach 2 - 2.7 times the basal value for H_2O_2 concentrations between 1 and 100 μM. Stimulation by H_2O_2 or free oxygen radicals was progressively inhibited until total suppression with arachidonic acid (0.75 - 5 μg/ml), and oxygen free radicals stimulated the release of ^{14}C arachidonic acid previously incorporated in isolated glomeruli. These latter two experiments demonstrated that the increase in PG synthesis in response to oxygen free radicals was due to activation of glomerular phospholipase. This effect which is likely to occur at an early stage of experimental glomerulonephritis could play a role in the mechanism of the inflammatory process.

Renal Metabolism

NEW FORM OF LYSOSOMAL ACID PHOSPHATASE IN PROLIFERATING RENAL CELLS INDUCED DURING POTASSIUM DEPLETION NEPHROPATHY. H. N. Aithal,* F. G. Toback, G. R. Rao,* G. S. Getz,* Departments of Biochemistry, Medicine and Pathology, University of Chicago, Chicago, IL.

Increased lysosome formation in renal medulla in potassium depleted (KD) rats is also associated with proliferation of cells of the inner red medulla (IRM). A possible relationship between increased lysosomal (Ly) enzyme activity and the proliferation of cells of IRM in KD rats has been explored in the present studies. Acid phosphatase (AP) activity was determined in Ly fraction since it is the typical marker enzyme of these organells. The activity was also measured in the microsomal (Mc) fraction because it is probably synthesized at this site. AP activity increased 3.3-fold and 4.1-fold in Ly and Mc fractions isolated from renal medulla from 4 week KD rats. Inhibition (50%) by Triton X 100 and insensitivity to tartrate (10 mM) distinguishes Mc AP activity from that of Ly. Dithiothreitol, 10 mM, caused 35% increase in activity only in the Ly fraction from KD rats. Resolution of AP activity solubilized with Triton X 100 by electrophoresis on polyacrylamide gels and staining for activity showed two major bands, one positively charged molecule with relatively low mobility and the other more negatively charged molecule in both Ly and Mc fractions from KD rats. However, only in Ly fraction from cells of IRM of 3 week (or longer) KD rats there appeared a new form of AP on the gel with increased mobility and negative charge. Thus, this new form of AP may play a role in the cell proliferation that occurs in this renal zone during potassium depletion.

TRANSFERRIN METABOLISM IN RENAL COMPENSATORY GROWTH. G.H. Beam*, M.R. Setayesh*, and L.M. Lowenstein Boston Univ. Med. Ctr., Boston, MA.

We have found that one of the renal growth factors in rat serum following uninephrectomy (UNx) is a 70,000 dalton globulin. The activity of the factor is measured by an early index of cell growth, the incorporation of ^{14}C-choline into phospholipids (C→PL) in Madin Darby canine kidney (MDCK) cells: the rate of (PL) production increases by 32% ($p < 0.001$) when cells are grown in serum drawn 24 hr following UNx, compared to that from sham-operated rats. Associated significant changes in uridine and thymidine metabolism also occur.

We investigated whether this factor could be a serum glycoprotein of known molecular structure. Since MDCK cells require transferrin, a 76,000 dalton glycoprotein, for growth, we measured iron metabolism in rats following 24 hr of renal compensatory growth. The unsaturated iron binding capacity (UIBC), an index of free transferrin, increased 33%, from 217 ± 11 SE to 288 ± 14 μg/dl ($p < 0.001$) in UNx serum, compared to serum from sham-operated rats. Conversely, the total iron decreased 45% in UNx serum, from 201 ± 15 SE to 111 ± 8 μg/dl ($p < 0.001$). However, the total iron binding capacity was similar in UNx and sham sera. These changes also occur early; within 1 hr of renal compensatory growth, rats had significantly increased levels of serum UIBC and decreased Fe++. The 1 hr compensatory serum also caused increased C→PL in MDCK cells. We suggest that initial events of renal compensatory growth involve changes in transferrin and iron metabolism, as well as in choline biosynthesis.

THE EFFECT OF ANTIDIURETIC HORMONE (dDAVP) ON IN VITRO SYNTHESIS OF PGE_2 BY RENAL MEDULLA IN THE DIABETES INSIPIDUS (DI) RAT. Thomas R. Beck*, Aviv Hassid* and Michael J. Dunn (intr. by R. Eckel). Case Western Res. Univ., Cleveland, OH.

Most acute stimuli of PG synthesis enhance phospholipase activity and the release of arachidonic acid. We assessed the possibility that the increase in PGE_2 excretion with chronic dDAVP treatment is due to increased renal medullary cyclo-oxygenase (CO) activity. dDAVP was given i.p. for 5 days via minipump (1.5ng dDAVP/h) to 12 wk male DI rats. Slices of renal medulla from treated rats (T) synthesized comparable amounts of PGE_2 to those from untreated (C) (0.51 ± .07 (T) vs. 0.62 ± .07 (C) ng PGE_2/mg wet weight/h; mean ± S.E.). Medullary microsomes from T rats, incubated with arachidonic acid (50μM) had synthetic rates of PGE_2 slightly greater than C microsomes (95.5 + 7.3 vs. 81.2 ± 4.6 ng PGE_2/mg protein/20', $p < .05$). To further evaluate CO activity slices were exposed to aspirin (ASA) 200μM, rinsed, and incubated for 2 h before the Ca++ ionophore A23187 (2μM) was added as a stimulus of endogenous fatty acid release. After ASA and A23187, T slices synthesized more PGE_2 than C slices (2.84 ± .38 vs. 1.94 ± .26 ng PGE_2/mg wet weight/30'; $p < .05$). Synthesis of PGE_2 by medullary microsomes prepared from animals 4 h after a single dose of ASA (500 mg/kg BW)was also greater in T than in C (49 ± 7.7 vs. 29.7 ± 5.8 ng PGE_2/mg protein/20', $p < .025$). In summary, dDAVP administration increased the in vitro synthesis of PGE_2 by medullary slices and microsomes, particularly when ASA was used to suppress basal CO activity. The increase in urinary PG excretion after chronic administration of dDAVP is probably due to induction of CO activity.

● RESTRICTION OF EXCHANGES BETWEEN MEDIUM AND LUMINAL MEMBRANE OF NEPHRON DURING INCUBATION OF RENAL SLICES. M. Bergeron, M.F. Arthus and C.R. Scriver, Dép. de physiologie, Université de Montréal, Montréal, Québec.

A controversy still exists regarding the ability of solute to gain direct access to the brush border (BB) membrane, from the medium, during incubation of renal slices (RS) and isolated collagenase-treated tubules. We have studied the hydrolysis of L-glutathion (GSH) and maltose in renal tissue in vitro. γ-glutamyl transpeptidase (GTP) and cysteinylglycine dipeptidase or maltase are involved in this process which occurs at the outer surface of the BB. We measured glucose formation from maltose or glycine release from (glycine-2-^{3}H)-labeled GSH incubated with rat kidney cortex homogenate, thin cortex RS (0.2 mm) or isolated tubules. The liberation of glycine was inhibited (74-83%) by serine borate (20 mM), indicating a GTP-dependent hydrolysis of GSH. With homogenates, GSH was effectively hydrolyzed (17,4 ± 0,6 nmoles of glycine formed/min mg protein. When RS were incubated, less GSH was degraded (3,5 ± 0,7 nmoles/min mg protein). Isolated tubules gave intermediate values (7,8 ± 0,4 nmoles/min mg dry weight) which were identical to homogenates of isolated tubules (7,6 ± 0,7). Similar data were obtained with maltase: when compared to homogenates (512 ± 22 nmoles glucose formed/min/mg of incubated protein), the hydrolysis of maltose by RS was markedly decreased (162 ± 12). The activity was higher in tubules (884 ± 48). In conclusion, our findings suggest that in isolated tubules the medium has access to the luminal membrane and imply that in RS the basolateral membranes are preferentially exposed.

● EFFECTS OF PARATHYROID HORMONE (PTH) AND GUANOSINE TRIPHOSPHATE (GTP) ON THE REGULATION OF RENAL CORTICAL ADENYLATE CYCLASE (AC) BY CALCIUM & MAGNESIUM. E. Bellorin-Font and K.J. Martin. Washington University, St. Louis, MO.

The renal effects of PTH involve AC activation. Previous studies indicated that Ca^{++} and Mg^{++} modulate the renal effects of PTH. The mechanisms involved remain unclear. We have examined the effects of Ca^{++}, Mg^{++} and GTP on PTH binding to receptors and activation of AC in purified canine renal cortical membranes. Specific binding of ^{125}I-Nle^8, Nle^{18}, Tyr^{34}, bPTH (1-34) amide was 25 ± 2% at equilibrium at 16° C. Half maximal displacement of the radioligand occurred at 2 nM syn b-PTH (1-34) the same concentration required for half maximal stimulation of AC activity. Basal AC was inhibited 50% by 0.5 mM Ca^{++}. In contrast, 50% inhibition of PTH stimulated AC occurred at 0.25 mM Ca^{++}. Inhibition of AC by Ca^{++} was further enhanced by increasing concentrations of PTH. This inhibition of PTH-stimulated AC activity by Ca^{++} was not due to decreased PTH binding. Therefore, an effect of PTH on the metal regulation of AC was studied. PTH markedly increased the affinity of AC for Mg^{++}, confirming an effect of PTH on the metal site of AC. Since GTP caused a similar effect on the affinity for Mg^{++} and since Ca^{++} competes with Mg^{++} for a common site, then GTP should also enhance the inhibition of AC by Ca^{++}. This was confirmed experimentally. The effect of GTP or PTH on the increased affinity for Mg^{++} and inhibition by Ca^{++} were not additive, suggesting a common mechanism of action. In conclusion, the Ca^{++} inhibition of PTH stimulated AC is not due to decreased binding of PTH but rather to an effect of PTH on the metal requirement for AC activation at the GTP regulatory site.

CELLULAR MECHANISMS OF VASOPRESSIN RESISTANT STATES Christos P. Carvounis and Georgia Carvounis*, Dept. of Medicine, Div. Nephrology and Hypertension, SUNY-Stony Brook, Stony Brook, N.Y. 11794.

We examined the pH dependence of vasopressin-resistant states in the toad urinary bladder. When vasopressin resistance was induced by removal of K+ from the bathing solution, by high serosal Ca^{++} (2mM) or by decreased osmolality (½NRingers), raising serosal pH from 7.4 (control) to 8.2 restored vasopressin sensitivity. Alkalinization of the serosal solution prior to the addition of vasopressin prevented the development of vasopressin resistance to the same maneuvers. Decreased response to vasopressin is also known to occur with prolonged vasopressin stimulation. Recovery of vasopressin sensitivity was found when the serosal pH was raised as late as 90 min following vasopressin administration. In all experiments ^{14}C-sucrose transport was not altered by serosal pH changes which argues against the induction of a "leaky" epithelium. Several vasopressin resistant states have been shown to be secondary to increased cytosolic Ca^{++}. Moreover, cytosolic Ca^{++} is known to be pH dependent. Therefore, we postulate that the reversal of vasopressin resistance by alkalinization of serosal bathing medium is mediated by alterations in cytosolic Ca^{++}. We also postulate that in vasopressin resistant states cell acidification ocurred following alteration of the serosal bath such as absence of K+ or following prolonged vasopressin stimulation, that led to increase in cytosolic Ca^{++} and therefore vasopressin resistance or down-regulation. Addition of OH-(serosal alkalinization) presumably normalized cytosolic Ca^{++} via increasing cell pH and rendered the epithelia once more sensitive to vasopressin.

SUCCINATE UPTAKE AND METABOLISM IN THE INTACT DOG KIDNEY. Francis P. Chinard. CMDNJ-New Jersey Medical School, Depts. of Medicine & Physiology, Newark, NJ, 07103.

Indicator-dilution procedures can provide information on in vivo aspects of renal transport and metabolism not accessible from studies of isolated cells or tubules. In this preliminary investigation of the renal handling of succinate, a bolus containing T-1824, creatinine, labelled succinate and (on occasion) THO is injected into the renal artery. A fraction, equal to the filtration fraction, enters glomerular fluid. Of the amount injected, whether 1,4 or 2,3 labelled, only .01 appears in the urine. In the transit from renal artery to vein, entry of labelled material into cells at the antiluminal border is indicated by upslope extractions of 0.6 -0.8 for each set of labelled positions relative to creatinine(used as flow limited reference). With ^{14}C in the 2,3 positions, less than .01 is recovered in the renal vein as $^{14}CO_2$ With ^{14}C in the 1,4 positions, about 0.6 of the label is recovered as $^{14}CO_2$. The data indicate that: 1)uptake of succinate at the antiluminal pole is substantial, 2) succinate undergoes more than single decarboxylation, 3) the residue is incorporated into intracellular reactions and pools,4)the time constant for the production of CO_2 from succinate carboxyls is of the order of 1 to 2 seconds.

DIFFERENT QUANTITATIVE EFFECTS OF GLUCAGON ON GLOMERULI AND TUBULES IN INCREASING PRECURSOR INCORPORATION INTO RNA IN EARLY STREPTOZOTOCIN (STZ) DIABETES. Pedro Cortes,Kumar Venkatachalam,* Francis Dumler,Nathan W. Levin,and Jose Goldman.* Henry Ford Hospital,Dept. of Medicine, Detroit, MI.

Incorporation of ^3H-orotate into RNA(% ^3H inc→RNA)is increased both in the renal cortex and isolated glomeruli in early STZ diabetes, probably reflecting increased pyrimidine nucleotide and/or RNA synthesis. Hyperglucagonemia(HG)may be the major factor causing this increase in the glomeruli (Kidney Int. 16:790;1979). To define whether glucagon has a similar effect on the renal cortex(95% tubules)we studied three groups of diabetic rats: untreated(D),insulin(0.5 U/day)treated (D+I) and insulin(0.5 U/day)and glucagon(0.86μg/day)treated (D+I+G). Insulin and glucagon were given as continuous intravenous infusions for 38 hr starting 10 hr after STZ injection. Renal cortices were obtained 48 hr after STZ,following a 2 hr infusion of ^3H-orotate. Glomeruli were separated from pooled renal cortices. Results are given as mean±SEM.

	Plasma Glucose (mg/dl)	Plasma Insulin (μU/ml)	Plasma Glucagon pg/ml	% ^3H inc→RNA/mg DNA Glomeruli	Cortex
D	430±10	27±4	280±33	0.196	4.36±0.2
D+I	459±4	51±5	166±12	0.172	3.82±0.16
D+I+G	426±10	57±3	290±37	0.277	4.14±0.22

Insulin replacement resulted in a similar decrease in % ^3H inc→RNA in glomeruli(12%) and renal cortex(14%). However, restoration of HG resulted in a greater increase in the ^3H inc→RNA in glomeruli(16%)than in renal cortex(8%). HG has a greater effect on glomeruli than tubules in increasing precursor incorporation into RNA in early STZ diabetes.

● SUPPORT OF RENAL FUNCTION BY FATTY ACIDS DERIVED FROM RENAL TISSUE LIPIDS. Julius J. Cohen* & Manasses C. Fonteles. Dept. Physiol., Univ. of Rochester, Rochester, N.Y.

The renal tissue lipids contain a large store of free fatty acids (FFA) which may either be a reserve of substrate or could be constantly turning over and be a source of substrate for support of normal function. However, no information is available as to whether FFA in tissue lipids can be used for support of function.

In order to determine whether the oxidation of free fatty acids (FFA) derived from renal tissue lipids can support renal function, we perfused isolated rat kidneys with a substrate-free Krebs Ringer bicarbonate solution containing 6 gm% of fatty acid-free albumin. We measured GFR, $\%\dot{T}\text{-}Na^+$, $C\text{-}H_2O$ and $\dot{Q}\text{-}O_2$ from 15 to 99 min after cannulation of the renal artery.

During substrate-free perfusion mean $\%\dot{T}\text{-}Na^+$ was ∿45%. When $1x10^{-4}$ M 2-tetradecyl glycidic acid (2-TDGA), a specific and irreversible inhibitor of long-chain acyl carnitine transferase I (extramitochondrial), was added to the perfusate, there were significant decreases in $\%\dot{T}\text{-}Na^+$ (-20%) and $\dot{Q}\text{-}O_2$ (-50%). In the absence of 2-TDGA there were no significant changes in $\%\dot{T}\text{-}Na^+$ or $\dot{Q}\text{-}O_2$ with time. During perfusion with 5 mM lactate, $\%\dot{T}\text{-}Na^+$ increased to ∿80%; however, when 2-TDGA was added, no decrease in $\%\dot{T}\text{-}Na^+$ or $\dot{Q}\text{-}O_2$ occurred. Thus 2-TDGA does not inhibit renal metabolism or function in the presence of a substrate which does not require long-chain acyl carnitine transferase for its utilization. From measurements of $C\text{-}H_2O$ the inhibitory effect of 2-TDGA on $\%\dot{T}\text{-}Na^+$ was localized to the proximal tubule. We conclude that FFA derived from renal tissue lipids can support a significant portion of proximal $\dot{T}\text{-}Na^+$.

● ASSOCIATION BETWEEN GLUCONEOGENESIS (GNG) AND OXIDIZED NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD^+) IN RENAL CORTEX (RC). S. Czekalski,* S.-Y.L. Ou,* S.A. Kempson, F.G. Knox, and T.P. Dousa: (intr. by C.G. Strong). Mayo Clinic, Rochester, MN.

Some stimuli (e.g. parathyroid hormone, starvation), which decrease proximal tubular reabsorption of phosphate (Pi) are known to enhance rate of GNG in RC. Since we recently found that NAD^+ inhibits RC brush border membrane (BBM) transport of Pi, we now explored whether rate of GNG in RC is associated with changes of NAD^+ content. Substrate-depleted rat RC slices were incubated without or with added (10 mM) substrates L-glutamate (L-Glu) or α-ketoglutarate (α-KG). Inclusion of L-Glu and α-KG increased ($P<0.005$) both rate of glucose production (Δ+526% and Δ+1261% resp.) and tissue level of NAD^+ (Δ+48% and Δ+52% resp.). Inhibitors of GNG, quinolinate (QA) and 3-mercaptopicolinate (3-MPA), decreased both glucose production (Δ-69% and Δ-84% resp.) and NAD^+ level (Δ-14% and Δ-21% resp.). Unlike NAD^+, levels of ATP in RC did not change with rate of GNG. GNG was also decreased in RC slices of rats infused QA and 3-MPA in vivo, but to a lesser degree. RC slices were incubated with or without L-Glu, then fractionated, and NAD^+ measured in cytosolic (10^6x g supernate) and in particulate (10^6x g pellet) fractions of homogenate. Incubation with L-Glu caused increase (Δ+55%; ($P<0.01$) of NAD^+ in cytosol, but not in particulate fraction. Results show that increased rate of GNG in RC is associated with increase in NAD^+, primarily in cytoplasm. This suggests that some phosphaturic stimuli exert their inhibitory effect on BBM transport and proximal tubular Pi reabsorption by stimulating GNG and increasing NAD^+.

INHIBITION OF GENTAMICIN UPTAKE IN RAT KIDNEY BY POLYCATIONS. S. Feldman*, C. Josepovitz*, M. Scott*, E. Pastoriza* and G.J. Kaloyanides. V.A. Medical Center, Northport, N.Y. and Div. of Nephrology and Hypertension, Dept. of Medicine, State Univ. of N.Y., Stony Brook, N.Y.

The uptake of gentamicin (G) into renal proximal tubular cells has been postulated to occur via a polycation transport system. To test this hypothesis we examined the effects of acute infusions of polycations on the uptake of G in renal cortex (RC) of anesthetized Sprague-Dawley rats. In initial studies we defined the uptake of G in RC as a function of filtered load. Increasing the filtered load of G from 16 ± 0.4 to 80 ± 6 and 157 ± 4 nmoles/min by raising plasma G concentration was associated with a linear increase of G in RC from 209 ± 10 to 577 ± 23 and 995 ± 51 nmoles/g cortex determined at the end of 140 min of infusion. When the filtered load of G was raised to 292 ± 11 nmoles/min, there was no further uptake of G in RC. Infusion of netilmicin, an aminoglycoside, and spermine, a polycation, at equimolar concentrations with gentamicin depressed the uptake of G in RC by 34% and 32% respectively, $p<0.01$. Infusion of polylysine (MW 3400) at 0.1 x the molar concentration of G depressed the uptake of G in RC by 70%, $p<.001$. Spermidine, cadaverine, putrescine and lysine were without effect. We conclude that gentamicin uptake into renal proximal tubular cells is mediated by a saturable polycation transport system. Analysis of structure-function relationships implicates the number of primary and secondary amines as important determinants of the affinity of polycations for the transport system.

ISOLATED RENAL TISSUE INVOLVEMENT IN NEPHROTIC HYPERCHOLESTEROLEMIA. Thomas A. Golper and Susan H. Swartz*. VA Medical Center, Portland, Ore.

The kidney handles mevalonic acid (MVA) in a unique fashion. Whereas the liver and other organs metabolize MVA to cholesterol, the kidney can shunt it to fatty acids for use as energy sources for Na reabsorbtion. In this nonsterol pathway the #5 carbon of MVA is converted to CO_2, whereas in the sterol pathway, that carbon is incorporated into the sterol rings. $^{14}CO_2$ production is an effective method of measuring nonsterol pathway activity when utilizing 5-^{14}C-MVA.

Male Sprague-Dawley rats rendered nephrotic by puromycin aminonucleoside had their kidneys perfused with Krebs-Henseleit-bicarbonate buffer containing albumin, glucose and 5-^{14}C-MVA. The % of MVA removed from the perfusate was 63±2 in 8 controls and 50±3 in 5 nephrotics ($p<.01$). The $^{14}CO_2$ recovered as a % of the MVA in the perfusate was 1.0±0.1 for controls, 0.4±0.1 for nephrotics ($p<.01$). Urinary recovery of MVA was 22±2% for controls and 15±1% for nephrotics ($p<.03$). Inulin clearances for the two groups were not different and correction for inulin clearance and kidney mass did not alter the statistical significance.

In conclusion, the isolated perfused nephrotic rat kidney metabolizes the cholesterol precursor MVA such that less is excreted, less is converted to fatty acids, and more is available for recirculation to the liver. Independent of hypoalbuminemia, abnormal renal MVA metabolism may play a role in nephrotic hypercholesterolemia.

● METABOLIC CHANGES ACROSS LIVER, GUT, MUSCLE AND KIDNEY WITH ACUTE ACIDOSIS IN THE DOG. A. Fine, Memorial University, St. John's, Newfoundland, Canada.

We have previously demonstrated that plasma glutamine (G) rises in acute acidosis (A.A.) in the dog (Fine et al. 1978 Clin. Sci. Mol. Med. 54: 503). The mechanism for this is unclear; G is metabolized/synthesized by many organs. Previous studies across these organs did not measure organ blood flow simultaneously so that net organ G metabolism in normal and in acidosis have not been established. Also the hepato-splanchnic bed is often considered as a whole whereas the gut and liver handle G differently. Alteration in glucose and alanine metabolism across these organs in A.A. have not been previously described. We have used electromagnetic flow probes to measure gut, liver, renal and hind-half blood flow in anesthetized dogs before and after acute HCL acidosis (5 mEq/kg). In the normal dog G is produced by muscle; the kidney, total hepato-splanchnic bed and gut extract it. Muscle and kidney produce alanine. In A.A. whole blood G and alanine rise by 20% and 50% respectively ($p < 0.001$) blood glucose falls by 15% ($p < 0.001$). Renal and muscle G metabolism is unchanged but there is decreased hepatic and hepato-splanchnic G extraction. Gut production of ammonia is increased ($p < 0.001$). Alanine production by muscle is increased by 40% ($p < 0.001$). Liver glucose production is reduced by 30% ($p < 0.001$). There is no apparent increase in muscle catabolism. It is concluded that more marked alterations in metabolism occur in A.A. in the dog *in vivo* than previously considered and that these changes are mainly confined to the liver and muscle.

● METABOLIC CHARACTERISTICS OF RENAL INSULIN UPTAKE. T.I. Gottheiner*, T. Tsao*, & R. Rabkin. Stanford Univ., Stanford, CA; Institute Medical Research, Santa Clara Valley Med. Center, San Jose, CA.

The kidney clears insulin from the circulation both by glomerular and peritubular clearance, thus exposing luminal and contraluminal tubular surfaces to insulin. We reported (JCI; 62, 169, 1978) that luminal insulin uptake is temperature sensitive and requires O_2; whereas contraluminal uptake does not need O_2. To further characterize insulin uptake, a study was performed with isolated rat kidneys perfused with an oxygenated albumin-electrolyte solution containing glucose, amino acids and insulin. In controls, total organ clearance of insulin (OCi) was 1336±51 (SEM) µl/min, GFR 1019±54 µl/min, peritubular clearance 317±56 µl/min, fractional excretion Na (FEna) 5.1±0.7% and fractional excretion insulin (FEi) 1.3±0.6%. Addition of inhibitors of glycolysis (iodoacetate), NA-K-ATPase (ouabain), and lysosomal degradation (chloroquine) was associated with a significant increase of FEi, (4.7±04, 6.4±1.4 and 13.9±2.4% respectively) and of FEna (28, 43 and 12% respectively). By contrast 5 mM acetazolamide with 1 mM furosemide increased FEna to 39%, without altering FEi. Analysis of all data revealed no correlation between FEna and FEi. None of the inhibitors altered OCi, GFR or peritubular clearance significantly.

Conclusions; 1) tubular insulin absorption is at least partly independent of Na reabsorption, 2) luminal insulin uptake, unlike contraluminal uptake, appears to have the metabolic features of a pinocytotic process followed by lysosomal degradation in that, a) it is temperature sensitive and dependent on energy fueled by ATP derived from oxidative metabolism and glycolysis, and b) it is inhibited by chloroquine.

● EFFECTS OF BICARBONATE ION AND pH ON THE pH GRADIENT IN RENAL CORTICAL MITOCHONDRIA. S.R. Hager* and D.P. Simpson. Dept. of Medicine, University of Wisconsin, Madison, Wisc.

To explain the changes produced by acute acid-base disturbances in levels of citric acid cycle substrates in renal cortex we proposed a mechanism based on the effects of pH and bicarbonate concentration ($[HCO_3^-]$) on mitochondrial anion accumulation (J. Clin. Invest. 63:704, 1979). We suggested that these effects might be related to modification of the pH gradient (ΔpH) across the inner mitochondrial membrane in acidosis and alkalosis. In the present study we determined intramitochondrial pH (pH_I) and ΔpH using [^{14}C]-5,5-dimethyl oxazolidine-2,4-dione in mitochondria from rabbit renal cortex incubated in bicarbonate buffered media containing rotenone. In the presence of an energy source (TMPD + ascorbate) and 5% CO_2 in the gas phase, with medium $[HCO_3^-]$ 5 mM and pH 7.0, pH_I was 7.62 ± 0.02 (n=8); with medium $[HCO_3^-]$ 40 mM and pH 7.7, $\overline{pH}_I$ was 8.07 ± 0.03 (n=8). As $[HCO_3^-]$ changed from 5 to 40 mM, $\Delta\overline{pH}$ fell steadily from 0.66 ± 0.02 to 0.33 ± 0.03. At a constant medium pH of 7.0, when $[\overline{HCO_3^-}]$ increased from 0 to 40 mM, ΔpH fell from 0.69 to 0.39. With constant $[HCO_3^-]$ and varying P_{CO_2}, increasing medium pH had no significant effect on ΔpH. Omission of an energy source practically abolished ΔpH. These results show that 1) $[HCO_3^-]$ is a major determinant of ΔpH; 2) variations in ΔpH occur with changes in pH and $[HCO_3^-]$ likely to occur within cells of renal cortex during disturbances of acid-base balance; and 3) these changes in ΔpH are sufficient in magnitude to account for the alterations in tissue levels of substrates seen in acute metabolic acidosis and alkalosis.

SIALIC ACID GLYCOCONJUGATES OF RAT KIDNEY BRUSH BORDER. Barry B. Kirschbaum, Medical College of Virginia, Division of Nephrology, Richmond, Va.

Polyanionic sialic acid containing glycoconjugates of the cortical tubule brush border may influence solute permeability across the luminal membrane. The present studies were conducted to quantitate and characterize membrane sialic acid. The kidneys of female retired breeder Sprague-Dawley rats were the source of brush border membrane fractions enriched approximately 13-fold in membrane marker enzymes. N-acetylneuraminic acid (NANA) was measured by the thiobarbituric acid assay of Warren after hydrolysis in 0.1N H_2SO_4 or 60 min incubation with Cl. perfringens neuraminidase which hydrolyzes 2,3-, 2,6-, and 2,8- α glycosidic linkages. Membrane NANA was 15.2±2.7 ug/mg protein (mean±S.D., N=8). 76% of total NANA was released by neuraminidase. 59% of total NANA was solubilized by the proteolytic enzyme papain. 75% of papain solubilized NANA was sensitive to neuraminidase while 60% of the NANA not released by neuraminidase was susceptible to papain digestion. 1.95±0.27 ug NANA/mg protein (N=5) or 13.6±2.2% of total NANA was extracted from the membrane by $CHCL_3$:CH_3OH(2:1). This organic solvent extractable NANA appeared to be entirely susceptible to Neuraminidase. Therefore, brush border NANA is found predominantly in papain sensitive glycoproteins, presumably membrane ectoproteins, but approximately 13% of NANA may be tentatively assigned to the ganglioside fraction. The 9.9% not released by both enzymes used sequentially may serve as an estimate of the sidedness of the vesicles formed in vitro by these membrane fragments.

PARTIAL CHARACTERIZATION OF RENOTROPHIC FACTORS IN URINE. R.H. Harris, C.F. Best*, and M.K. Hise*. Duke University, Nephrology Division, Durham, N.C.

We have reported that, in rats, continuous i.v. reinfusion of half the urine output for 24 h leads to increases in renal mass and in renal synthesis of protein and DNA. Dialysis of urine prior to its reinfusion does not block this renal growth stimulation. This suggests that the circulatory retention of poorly-dialyzable urinary factors is capable of stimulating renal growth. The present study was designed to further characterize this renotrophic activity in urine. A bioassay system was used, in which an assay rat received, over 24 h, an i.v. infusion of the total 24-h urine output (collected via bladder catheter) of a "donor" rat. As control, a matched littermate of the assay rat received the same volume of saline in 24 h. Following infusion, *in vitro* renal DNA synthesis rate (^{3}H-thymidine incorporation into cortical slice DNA) was determined. DNA synthesis response (DSR) was calculated as the ratio of urine-infused/saline-infused thymidine uptake.

Renal growth stimulation was evident in 21/22 assays, with DSR of 2.04 ± 0.23 ($p<0.001$). Upon fractionating the urine by ultrafiltration membranes, the fraction >50,000 MW showed DSR of 2.08 ± 0.29, greater than ($p<0.001$, n=7) DSR of 1.40 ± 0.20 for the fraction <50,000. The fraction <10,000 gave no response. Heated urine (100 °C, 30 min) showed DSR of 2.01 ± 0.43, less than ($p<0.001$, n=7) DSR of 2.56 ± 0.46 of unheated urine. Thus, a major portion of urinary renotrophic activity appears attributable to factors >50,000 MW, and a lesser portion between 10,000-50,000 MW. In addition, a major portion of the activity appears due to heat-stable factors.

● PROSTAGLANDIN (PG) SYNTHESIS BY ISOLATED RABBIT CORTICAL COLLECTING TUBULES (CCT). M.A. Kirschenbaum, A. Lowe*, W. Trizna*, and L.G. Fine. Division of Nephrology, UCLA School of Medicine, Los Angeles, CA.

Since PG's are tissue hormones, their influence on tubular NaCl and water transport may depend on their ability to be synthesized locally at their site of action. Although previous studies have demonstrated that renal medullary interstitial cells can synthesize PG's in vitro, there has been no direct evidence for the tubular epithelial synthesis of these lipids. Studies were performed to evaluate the ability of isolated CCT segments to convert octatritiated arachidonic acid (AA) to several PG's. Equal lengths of rabbit CCT's were isolated by dissection and pre-incubated with dexamethasone (50μM). Cold + tritiated AA (450μM total) were then added to the incubation medium with either a cyclo-oxygenase inhibitor (indomethacin, meclofenamate, or ibuprofen) or its vehicle. PG's were identified by thin layer chromatography. AA metabolites produced in order of decreasing quantities were PGE_2, TxB_2, $PGF_{2\alpha}$, and PGI_2/6-keto-$PGF_{1\alpha}$. In addition, PGA_2 and hydroxylated fatty acids were identified. Cyclo-oxygenase inhibitors decreased the counts in all of the PG peaks from 37% for PGI_2 to 50% for PGE_2. In summary, rabbit CCT are capable of synthesizing all of the major PG's and this synthesis can be decreased by various cyclo-oxygenase inhibitors.

● SITES OF PRODUCTION OF 1,25(OH)$_2$D$_3$ AND 24,25(OH)$_2$D$_3$ ALONG THE RAT NEPHRON. K. Kurokawa, H. Kawashima* and S. Torikai*. VA Wadsworth Med. Ctr. and UCLA Sch. Med., Los Angeles, CA

Kidney is the only site of 1,25(OH)$_2$D$_3$(1,25D) and the major site of 24,25(OH)$_2$D$_3$(24,25D) production from 25(OH)D$_3$(25D). Previous studies in single nephron segments showed 1,25D production in proximal convoluted tubules(PCT) and thick loop cortex in chick kidney and in PCT and proximal pars recta(PR) in fetal rabbit kidney. Data regarding the site of 1,25D production in mature mammalian kidney are not available. Further, intrarenal sites of 24,25D production is not known. In the present study we examined 1,25D and 24,25D production by isolated nephron segments from vitamin D deficient(-D) rats and normal rats given 1,25D for 7-9 days(+D). Isolated tubules were incubated at 37°C for 60 min in a modified Hanks buffer containing ^{3}H-25D. Following extraction by chloroform-methanol, 1,25D and 24,25D were separated by thin layer chromatography and their authenticity verified by HPLC. Nephron segments tested include glomerulus, PCT, PR, medullary and cortical thick ascending limb of Henle's loop, distal tubules, cortical and medullary collecting tubules. 1,25D production occurred only in PCT of -D rats at a rate of 0.70± 0.05(SE, n=10) fmol/mm/hr. By contrast, 24,25D production was detectable only in PCT and PR of +D rats at rates of 0.62±0.07 and 1.09±0.23 fmol/mm/hr, respectively. The results thus define the distribution of 1,25D and 24,25D production along the rat nephron: PCT is capable of producing both 1,25D and 24,25D and PR produces only 24,25D under the present experimental conditions. Data add new information on renal regulation of vitamin D metabolism and suggest possible separation of systems responsible for 1,25D and 24,25D production.

● THROMBOXANE A$_2$ - MAJOR PROSTAGLANDIN OF HUMAN HYDRONEPHROTIC KIDNEY. Aubrey R. Morrison and Fergus Thornton.* Washington University School of Medicine, St. Louis, MO. and Alan Blumberg* and E. Darracott Vaughn, Department of Surgery, Cornell University, New York.

Human renal tissue has been reported to metabolize arachidonic acid to various prostaglandins $PGF_{2\alpha}$>6K$PGF_{1\alpha}$>PGE_2>TxB_2 (JBC 255:2472-2475 1980). Earlier work in our laboratory with experimental obstructive uropathy in rabbits has demonstrated the production of thromboxane A_2 by the obstructed kidney. We therefore evaluated the metabolic potential of human hydronephrotic tissue by radiochemical and chromatographic methods. Microsomal preparations of human cortical renal tissue incubated with [^{14}C] arachidonic acid produced as the major product thromboxane B_2. The total metabolic conversion was 3-5% using L-epinephrine 1.2 mM as cofactor. We incubated cortical microsomes from hydronephrotic kidneys with [^{14}C] PGH_2 to bypass the cyclooxygenase and compared metabolic end products with microsomes obtained from control kidneys (normal tissue from tumor nephrectomy). Hydronephrotic tissue converted PGH_2 to HHT>TxB_2>6K$PGF_{1\alpha}$>PGE_2>$PGF_{2\alpha}$. Inhibition of thromboxane synthesis with imidazole 5 mM altered the end products such that 6K$PGF_{1\alpha}$ became the prominent prostaglandin found and distribution was 6K$PGF_{1\alpha}$>PGE_2>HHT>$PGF_{2\alpha}$>TxB_2. On the other hand in the control microsomes in absence of imidazole PGH_2 gave HHT>PGE_2>TxB_2>$PGF_{2\alpha}$>6K$PGF_{1\alpha}$ and with imidazole PGE_2>HHT>$PGF_{2\alpha}$>6K$PGF_{1\alpha}$. Thus these experiments indicate an enhanced capacity of human hydronephrotic tissue to form thromboxane A_2 and 6K$PGF_{1\alpha}$, the latter clearly expressed after inhibition of thromboxane synthesis.

● DEMONSTRATION OF ENHANCED RENAL AMMONIAGENESIS BY ACUTE ACID AND SALINE LOADS IN CONSCIOUS DOGS. T.W. Meyer,* M.A. Arcangeli,* and T.A. Aoki*: (intr. by H.S. Solomon). Harvard Med. Sch., Boston, MA.

Increased ammonia production from glutamine by the dog kidney is said to occur only after several days of adaptation. We tested this hypothesis by examining the acute response to intravenous acid and isotonic saline loads in awake dogs with chronically implanted arterial and renal vein catheters. Total ammonia synthesis (TNH_3) is defined as the sum of ammonia added to urine (UNH_3) and to renal vein blood ($RVNH_3$). Within two hours of a small acid load (HCl, 2.2 meq/kg) there was an 80% increase in TNH_3 with a stoichiometric increase in glutamine uptake (Gln). (Data are means, n=6, † p< .05).

	Art pH	Urine pH	UV ml/m	UNH_3	$RVNH_3$ µmoles/m	TNH_3	Gln
cont.	7.37	6.57	.3	18	20	38	19
acid	7.34†	6.06†	1.7†	54†	17	71†	35†

When dogs fed acid were given a saline load (4.5% body weight in 40 min) there was again an increase in ammonia production from glutamine within two hours.

	Art pH	Urine pH	UV ml/m	UNH_3	$RVNH_3$ µmoles/m	TNH_3	Gln
cont.	7.35	5.92	.2	46	14	59	19
saline	7.37†	5.91	6.0†	83†	16	98†	48†

Arterial pH fell only slightly in the acute acid loaded dogs and actually rose in the saline loaded dogs. Arterial glutamine levels did not change in either experiment. We conclude that ammonia production by the dog kidney can increase acutely and that these increases are better correlated with urine pH and flow (UV) than with arterial pH or glutamine level.

LACTIC DEHYDROGENASE (LDH) ISOENZYME ACTIVITY IN THE HYDRONEPHROTIC RAT KIDNEY. J.B. Nanninga, L. Oliver*, and Chung Lee*. Northwestern University Medical School, Department of Urology, Chicago, Illinois 60611.

Previous studies in the obstructed kidney have demonstrated a shift from aerobic to anaerobic metabolism. One method of studying renal metabolism is to determine the tissue LDH isoenzyme pattern. In tissues which are undergoing a shift from aerobic to anaerobic metabolism, there is a shift from the LDH-1 to LDH-5 fraction. Short term renal obstruction of 7-10 days has been shown to produce an increase in the LDH-5 fraction.

To study the effect of obstruction on the renal LDH isoenzymes over a 6 week period we ligated the ureter of one kidney in a group of rats. A separate group underwent a sham operation. The animals were sacrificed at 2,4,and 6 weeks and the renal tissue analyzed for LDH isoenzyme activity in the hydronephrotic(H) group, contralateral(C) kidneys, which underwent compensatory hypertrophy, and sham group.

In the sham group the mean value for the LDH-5/LDH-1 ratio was 1.4. The LDH-5/LDH-1 values for the H and C kidneys were as shown.

	2 weeks	4 weeks	6 weeks
H	4.5*	3.0*	4.7*
C	1.2	1.3	1.4

(*difference is signicant at less than 0.025)

The results demonstrate a persistent change in the LDH-5/1 ratio when the kidney is obstructed for up to 6 weeks and provides a biochemical marker for the hydronephrotic kidney. The LDH activity in the sham group kidneys was not significantly different from the compensatory hypertrophy kidneys.

EVIDENCE FOR ACTIVATION OF THE RENAL GLUTAMATE DEHYDROGENASE PATHWAY IN INTACT ACIDOTIC DOGS.
A. Risquez,* J.V. Lombardo,* D.S. Gaydos,* and H.G. Preuss. Georgetown Univ., Dept. of Med. & Pathol., Washington, D.C.

Infusing glutamine into chronically acidotic, normal, and acutely alkalotic dogs enhanced renal ammonia production; more was formed as glutamine loading increased. In 4 acidotic dogs, the ratio of ammonia produced to glutamine extracted by the kidneys during exogenous glutamine loading was 1.93 compared to 0.99 for 5 alkalotic dogs and 1.23 for 2 control dogs. Little glutamate and alanine were released into the renal vein in acidotic dogs; whereas over 50% of the exogenous glutamine extracted in acutely alkalotic dogs could be accounted for as glutamate and alanine released into the renal vein. Renal glutamate concentrations were not elevated in acidosis compared to alkalosis despite greater deamidation. When glutamine infusions increased renal ammoniagenesis in acutely alkalotic and control dogs to levels seen in chronically acidotic dogs receiving no exogenous glutamine, approximately 4 to 6 times more glutamate was released from the kidneys. Infusing alanine into 7 chronically acidotic dogs enhanced ammoniagenesis significantly ($p < 0.01$), while lesser augmentation was seen in 3 control dogs and no augmentation was seen in 6 acutely alkalotic dogs. The increases were secondary to enhanced glutamate deamination, not secondary to any changes in glutamine extraction and/or transaminase activity. We conclude that the glutamate dehydrogenase pathway is more active in intact acidotic dogs than in control and alkalotic dogs and that the amino nitrogens of glutamine and other amino acids contribute significantly to adaptive ammoniagenesis.

EFFECT OF HIGH K^+ ON RENAL NH_3 PRODUCTION.
S. Sastrasinh* and R.L. Tannen, University of Michigan, Ann Arbor, Michigan.

Studies in the whole organism have suggested that high K^+ inhibits renal NH_3 production; however, it is unclear whether this results from an intrinsic adaptation to a high K^+ intake and/or to a direct effect of ambient K^+. When renal cortical slices are incubated in vitro with a high K^+ concentration, the effect on NH_3 production is controversial. Furthermore, in contrast to the isolated perfused kidney under conditions of acute acidosis, NH_3 production by renal cortical slices does not appear to reflect changes in vivo. Therefore, to investigate the influence of high K^+ on renal ammoniagenesis isolated kidneys from rats fed with normal diet (control) and high K^+ diet (K^+-adapted) were perfused for 90 minutes with 5 mM glucose and 0.5 mM glutamine. Midway during perfusion perfusate $[K^+]$ was increased from 5.0 to 9 mM by the addition of KCl. During the first 45 minutes of perfusion kidneys from K^+ adapted rats (n=8) excreted more K^+ than Controls (n=16); ($2.14 \pm .26$ vs. $0.57 \pm .04$ μmol/min, $p < .001$) but there was no difference in NH_3 production ($2.08 \pm .12$ vs. $2.04 \pm .17$ μmol/min/g dry wt.). When the concentration of K^+ in the perfusion medium was increased NH_3 production fell in both groups of rats (Controls: $-0.63 \pm .27$ μmol/min/g dry wt. (n=11) $p < .05$; K^+-adapted: $-0.60 \pm .40$ μmol/min/g dry wt (n=5) (N.S.) No significant change in NH_3 production occurred in kidneys perfused with 5.0 mM $[K^+]$ for 90 minutes ($+ 0.37 \pm .14$/μmol/min/g/dry wt., N.S.)

Thus no significant change in ammoniagenesis by the whole kidney was detected in the K^+ adapted state, however, a high ambient K^+ concentration significantly lowered renal NH_3 production.

REGULATION OF PLASMA ALDOSTERONE CONCENTRATION IN THE PRESENCE OF ACUTE CHANGES IN ACID BASE BALANCE.
D.G. Sapir, R.N. Wyndham,* and C.R. Cooke. The Johns Hopkins Hospital, Baltimore, Maryland.

To determine whether plasma aldosterone concentration is influenced by acute changes in acid base balance, anephric hemodialysis patients were dialyzed with solutions containing HCO_3^- 17.5 mEq/L (A) or 35 mEq/L (B). Corresponding dialysate Cl^- concentrations were 117.5 and 100 mEq/L respectively while K+ concentration was 5.0 mEq/L in both solutions. Each patient was studied twice, once with solution A and once with B. Mean±SEM changes (end-beginning) in acid base parameters and plasma aldosterone and K+ concentrations during hemodialysis were as follows:

SOL'N	BEFORE pH	AFTER pH	ΔH+	ΔHCO3⁻	ΔpCO2
A	7.33	7.19*	+17±2*	-7±1*	-4.0±1*
B	7.28	7.37*	-11±4*	+3±1	-0.3±2

	ΔK	ΔALDO
A	+0.2±0.2	+2.3±1.1
B	-0.6±0.3	-0.5±1.1

*$p<0.01$

Changes in plasma aldosterone did not correlate with changes in plasma H+ concentration nor with changes in plasma Na+, Cl^- or HCO_3^- concentrations. Changes in plasma aldosterone did correlate with changes in plasma potassium concentrations when all studies were examined.

Thus, large changes in extracellular H+ ion concentration did not result in changes in plasma aldosterone concentration nor disrupt its correlation with plasma K+ concentration.

URINARY INHIBITOR OF RENAL AMMONIAGENESIS DURING ACUTE ACIDOSIS.
S. Sastrasinh* and R.L. Tannen (Intro. by F.K. Port), University of Michigan, Ann Arbor, Michigan.

We have previously shown in isolated perfused rat kidney that acute metabolic and respiratory acidosis stimulate renal ammoniagenesis to a similar degree and that this effect is abolished if the urine is allowed to drain back into the perfusate (Proc. Amer. Soc. Nephrol., 70A, 1979). Although most of the known factors influencing NH_3 production could not account for the inhibition of renal ammoniagenesis observed with urine infusion, the possibility could not be excluded that NH_3 excreted in the urine acts as inhibitory substance. To test this hypothesis further we added NH_4Cl to the perfusate midway during a 90 minute perfusion with 5 mM glucose and 0.5 mM glutamine. Perfusate pH was lowered to 6.8 by altering the pCO_2 at the same time. A control group was subjected to acute respiratory acidosis without the addition of NH_4Cl.

Perfusate NH^+_3 level during respiratory acidosis in the NH_4Cl studies was markedly higher than in the controls ($1.21 \pm .09$ vs. $0.52 \pm .07$ mM. $p < .001$) but NH_3 production increased comparably in both groups (NH_4Cl studies: $1.61 \pm .22$ to $2.75 \pm .40$ μmol/min/g dry wt, $p < .05$; Controls: $1.69 \pm .18$ to $2.70 \pm .25$ μmol/min/g dry wt, $p < .001$). There were no differences in perfusate pH, glutamine or K^+ level between the two groups.

Therefore, acute respiratory acidosis stimulated NH_3 production in the presence of perfusate NH^+_3 concentration which exceeded the value previously observed ($0.73 \pm .07$ mM) in the studies of acute respiratory acidosis combined with urine infusion. These findings indicate that the inhibitory factor excreted in the urine is not NH^+_3.

● pH CONTROL OF KIDNEY α-KETOGLUTARATE DEHYDROGENASE. Anton C. Schoolwerth, Kathryn F. LaNoue* and Wanda J. Hoover*. The Pennsylvania State University, Hershey, Pennsylvania.

Kidney cortex α-ketoglutarate (αKG) levels have been consistently observed to decrease abruptly and significantly in acute metabolic acidosis. These decreased levels may be of major importance in regulating enhanced ammonia synthesis since αKG has been shown to inhibit renal ammoniagenesis, probably by reducing mitochondrial glutamine entry and glutamate deamination. In order to determine the mechanism of decreased tissue αKG content in metabolic acidosis, studies were performed using isolated mitochondria from rat kidney cortex. The effect of medium pH on mitochondrial oxygen consumption from 0.1mM αKG as substrate was measured in the presence of ADP at pH values ranging from 7.6 to 6.6. A stepwise and progressive increase in αKG respiration was observed as pH was decreased from 7.6 to 6.6. Oxygen consumption from αKG was 144% greater at pH 6.6 than 7.6 (69 vs 28 nAtoms O/mg/min). To determine whether these results represented a direct pH effect on α-ketoglutarate dehydrogenase (αKGDH), the activity of the enzyme was measured at different pH levels in freeze-thawed mitochondrial extracts. αKGDH activity was inversely related to pH over the range pH 6.6-7.6. Kinetic analysis of αKGDH at two pH levels indicated that the Vmax was identical at pH 7.4 and 6.8. However, the apparent Km for αKG decreased from 0.38mM at pH 7.4 to 0.05mM at pH 6.8. These studies indicate that H^+ accelerates αKG metabolism by a direct effect on αKGDH. During acidosis in vivo, reduced tissue pH may lower αKG levels, thus decreasing feedback inhibition due to αKG and enhancing renal ammoniagenesis.

● LUMINAL AND ANTILUMINAL TRANSPORT IN DOG KIDNEY: EFFECT OF METABOLIC ACIDOSIS. M. Silverman, P. Vinay, L. Shinobu*, A. Gougoux and G. Lemieux. Dept. of Medicine, Univ. of Toronto and Renal Laboratory, Hotel-Dieu Hospital, Montreal.

Luminal and antiluminal transport of glutamine and glutamate was studied in normal, acutely and chronically acidotic dogs using the pulse injection multiple indicator technique. The single pass experiments yield estimates of unidirectional influx at each nephron surface. The kidney of normal dogs extracts 57% of the arterial glutamine load; 23% is due to luminal reabsorption and 34% to antiluminal uptake from the peritubular circulation. Total net extraction was determined from arteriovenous differences and blood flow measurement. In normal dogs net antiluminal flux was negative, indicating that at least part of the glutamine reabsorbed is returned to the renal vein. In acutely acidotic dogs the situation is similar but a 30 - 40% fall in renal hemodynamics (blood flow and GFR) causes secondary reduction in luminal and antiluminal uptake. In chronically acidotic dogs unidirectional luminal and antiluminal uptakes of glutamine are similar to that observed in normal animals, but calculated efflux across the antiluminal membrane is drastically reduced. These findings suggest that 1) a cellular transport mechanism for glutamine exists at the antiluminal pole of the renal tubule and dominates the luminal uptake process in normal animals; 2) cellular transport of glutamine does not play a role in the renal adaptation to metabolic acidosis; 3) the intrarenal utilization of glutamine acts as a metabolic sink thereby regulating its net uptake by the kidney; and 4) the total uptake of glutamine limits ammoniagenesis in this species.

LIGHT EMISSION BY ISOLATED RAT GLOMERULI. S.V.Shah Nephrol. Sect., VAH & Tulane Univ. Med. Ctr., New Orleans, Louisiana.

Phagocytic cells produce reactive oxygen species (ROS) in response to an appropriate stimulus. Since the presence of phagocytic cells in glomeruli is well documented, we examined the production of ROS, as quantified by luminol-amplified chemiluminescence (CL), in the resting and stimulated states [in response to phorbol myristate acetate (PMA)] from glomeruli and tubules from rat renal cortex. Glomeruli had a higher level of resting light emission compared to tubules (glomeruli $43\pm8\times10^3$, n=18; tubules $2.17\pm0.42\times10^3$, n=6 cpm/mg protein) and exhibited a significantly greater increase in CL in response to PMA (glomeruli $1675\pm200\times10^3$; tubules $31.93\pm3.26\times10^3$ cpm/mg protein). CL response in glomeruli showed an initial lag of 60-90 sec followed by rapid increase which reached a peak at 20 min with a slow decline thereafter. No response was obtained from boiled, sonicated or homogenized glomeruli. CL response was dose dependent in the range of 0.1-10 μg/ml with maximal stimulation between 5-10 μg/ml. In glomeruli Antimycin A, an inhibitor of mitochrondial electron transport, caused a significant (% change 40±8, n=6) inhibition of the PMA stimulated response; in contrast in leukocytes prepared from the same rats as used to prepare glomeruli, Antimycin A caused a significant (% change 48±6, n=3) increase in PMA stimulated CL response. These results indicate that glomeruli in response to an appropriate stimulus produce a light emitting response that is most likely related to production of ROS. ROS produced by glomeruli in response to immune injury may be important in the pathophysiology of glomerular diseases since ROS have been shown to affect biological processes potentially important in glomerular diseases.

● INSULIN RESISTANCE (IR) IN UREMIA: EVIDENCE FOR RECEPTOR AND POSTRECEPTOR DEFECTS. D Smith* and R DeFronzo, Yale Univ. Schl. Med., New Haven, Ct.

Tissue sensitivity to insulin (I), quantitated with the I clamp technique (plasma I=110±5 μU/ml), was reduced by 54% in 17 uremic subjects (3.8±0.2 vs 7.2±0.5 mg/kg·min). Previous studies from our lab have shown that insulin binding (IB) is variably decreased in uremia. However, whether a postreceptor defect also contributes to the IR is unknown. To further examine the contribution of decreased IB to the IR, we constructed dose response curves relating in vivo I-mediated glucose (G) metabolism to plasma I. Since I action is associated with IB to a small percentage (∿10%) of available receptors, with a receptor defect normalization of the I response would be expected if a sufficiently high I conc is attained; in contrast with a postreceptor defect decreased insulin response would be expected at all I conc. Plasma I was raised by 100, 500, 1000 μU/ml while maintaining plasma G constant at basal levels. Under these steady-state conditions the amount of G metabolized (M) equals the G infusion rate and is a measure of tissue sensitivity to I. At all three I plateaus M was significantly reduced ($p<0.01$) in uremics (3.4±0.3 vs 7.2±0.5; 5.9±0.2 vs 9.9±0.5; 7.0±0.5 vs 10.9±0.5 mg/kg·min). These data represent a rightward shift in the dose response curve relating plasma I to M and a failure to normalize I-mediated G metabolism even at maximally effective plasma I. These results are the predicted consequence of a postreceptor defect in I action. Conclusion: although insulin binding may be decreased in uremia, a postreceptor defect plays a major role in the IR of uremia.

● INSULIN DEGRADATION BY LUMINAL AND BASOLATERAL RENAL TUBULAR MEMBRANES. Z. Talor*, D.S. Emmanouel and A.I. Katz. Department of Medicine, University of Chicago, Chicago, Illinois.

Clearance experiments suggest that renal insulin (Ins) handling involves in addition to filtration and tubular reabsorption, also uptake from peritubular blood. However, autoradiographic and microperfusion studies failed to show participation of contraluminal uptake in renal Ins metabolism. We studied the degradation of ^{125}I-labeled monoporcine monocomponent Ins (specific activity 0.7 mCi/μg) by luminal (L) and basolateral (BL) tubular membranes prepared from rabbit kidney cortex homogenates (H) by differential and gradient centrifugation and ionic precipitation techniques. Marker enzyme activities (Na-K-ATPase for BL membranes and maltase for L membranes) were enriched 9 ± 1 fold and 15 ± 2 fold, respectively vs H. Ins degradation was determined by the measurement of TCA precipitable radioactivity after incubation of the membranes with physiologic concentrations of the hormone (0.6 ng/ml) at 37°C, pH 7.4. Degrading activity was higher with L (19.7 ± 0.7 pg/mg protein/min) but BL were also capable of substantial Ins degradation (6.1 ± 0.9 pg/mg protein/min). Ins degrading activity of BL could not be attributed to lysosomal contamination because at pH 7.4 purified lysosomes account for only 4% of Ins degradation by BL, nor to L, since the rate of Ins catabolism by BL was significantly ($p<0.02$) higher than that which could be attributed to L cross-contamination. The results indicate that basolateral membranes of renal tubular cells can degrade Ins, and therefore support the existence of a peritubular uptake mechanism in the renal handling of this hormone.

● ISOLATION OF A PURE SUSPENSION OF RAT PROXIMAL KIDNEY TUBULES. Patrick Vinay, Guy Lemieux and André Gougoux. Renal Laboratory, Hotel-Dieu Hospital and Department of Medicine, University of Montreal, Montreal, Quebec.

A suspension of cortical tissue fragments prepared by collagenase digestion of renal cortex obtained from fed and chronically acidotic (NH_4Cl) rats was separated in four bands on a PERCOLL density gradient. By microscopic examination, vital staining with trypan bleu, and histologic staining technique (PAS) the band F_4 was shown to contain only (>98%) proximal tubules, while the band F_1 was significantly enriched (≈70%) with distal tubules with contamination by glomeruli, and short segments of proximal tubules. Intra/extracellular ratios for PAH of 15 were measured with the F_4 band and of 2 in F_1 band. ATP was 1.4 μmol/g and 2.8 μmol/g in the F_4 and F_1 band respectively and was stable for at least 60 minutes. A F_4/F_1 activity ratio for the proximal cytoplasmic phosphoenolpyruvate carboxykinase enzyme of 2.63 and 4.29 was observed in normal and acidotic rats respectively. In contrast, a F_4/F_1 ratio of 0.12 and 0.22 was observed for the distal cytoplasmic hexokinase enzyme. The proximal F_4 band was shown to be gluconeogenic (L-glutamine or L-lactate 2.5 mM as substrates) and to adapt to metabolic acidosis. The distal F_1 band was shown to be glycolytic (glucose 2.5 mM) with no changes with acid base status. All fractions were shown to metabolize glutamine, but the metabolic fate of this amino acid was different in proximal and distal structures. This preparation therefore allows to study the metabolism of an homogeneous population of proximal tubular fragments, and can be used to obtain some information on enzymes location within the nephron.

● SODIUM INDUCES GROWTH OF KIDNEY EPITHELIAL CELLS (KEC) IN CULTURE. F. G. Toback, Molecular Biology Laboratory, The Salk Institute, San Diego, CA, & University of Chicago, Chicago, IL.

Increased cation uptake and cell proliferation occur in kidneys of potassium-depleted rats. To test if cations could mediate early events during the onset of renal growth, Na^+ was added to cell cultures of the African green monkey kidney epithelial line (BSC-1). The effect of NaCl on DNA synthesis and cell growth was studied in quiescent, high-density cultures to simulate the low proliferative activity of kidney cells in vivo. Addition of 5 to 25 mM NaCl to the culture medium progressively increased [^{3}H] thymidine incorporation into DNA up to 41% in a concentration-dependent manner during serum growth stimulation. This result was not mediated by an increment in Cl^- concentration or osmotic pressure because it could not be replicated by addition of equiosmolar LiCl or sucrose. Autoradiography revealed that the increment in DNA synthesis induced by Na^+ represented an increase in the number of cells synthesizing DNA. The effect of Na^+ on cell growth was assessed by adding 25 mM NaCl to confluent cultures and the number of cells per dish counted for 4 weeks. Na^+ increased the growth rate and final cell density under these conditions. NaCl retarded growth when cultures were sparse, but as confluence was achieved the growth rate surpassed that in control cultures and remained elevated as cells grew to high density.

Increased Na^+ in the medium of high-density KEC cultures induced initiation of DNA synthesis in more cells and faster cell growth. This capacity of Na^+ to initiate DNA synthesis was serum and cell-density dependent. Thus Na^+ may act as a mediator of events that initiate cell proliferation.

● FEASIBILITY OF USING ^{31}P NMR TO STUDY KIDNEY METABOLISM IN VIVO. M.W. Weiner, K. Burke,* K. Green,* D. Wemmer,* N. Wade Jardetsky,* and O. Jardetsky.* Dept. of Medicine, VA Med. Ctr., Univ. of Calif. San Francisco and Magnetic Res. Lab. Stanford Univ.

^{31}P NMR spectroscopy has been used to identify the phosphorous residues associated with adenine nucleotides, creatine phosphate, and inorganic phosphate. Previous investigators have used ^{31}P NMR to measure these compounds in muscle, heart and kidney which were perfused in vitro. The present experiments were designed to determine if ^{31}P NMR spectra could be obtained from the kidney in vivo. Solenoid radiofrequency coils were placed around the left kidney of Sprague Dawley rats. The wires were exteriorized at the back of the neck. After recovering from surgery the animals tolerated the coils well for several weeks. Animals with chronically implanted coils were studied in a Varian XL 100 magnetic resonance spectrometer with a Nicolet 1180 Data System operating 40.5 MH_z. Control spectra showed peaks for inorganic phosphate, hexose phosphates, and the three phosphates of ATP. The signal to noise ratio was lower than that reported for organs perfused in vitro. This is probably due to the water in the surrounding tissues. Administration of fructose (40 μmol/g body weight IP) produced a decrease in the β ATP peak and an increase of the hexosephosphate peak. The NMR procedure did not produce any detectable ill effects. It is concluded that chronically implanted radiofrequency coils can be used to obtain ^{31}P NMR spectra from the kidneys of intact living animals. Thus, ^{31}P NMR may be used to measure renal phosphate metabolism in vivo in a continuous and non-destructive fashion.

EVIDENCE FOR SHORT-CIRCUITING OF PAH IN THE SUPERFICIAL CORTEX OF THE RAT KIDNEY. S. Weinstein, R. Klose* And A. Kumar*. Dept. of Medicine, Div. of Nephrology and Hypertension, SUNY-Stony Brook, Stony Brook, N.Y. 11794.

Early postglomerular efferent vessel (EV) blood contains an admixture of early and late proximal tubular reabsorbate. Tubular secretion of organic acids, such as PAH, occurs primarily in the late proximal tubule. Thus, extraction of these compounds should occur preferentially from EV blood. This may disproportionately reduce their delivery to those portions of the tubule supplied by the downstream peritubular capillaries. To study this, proximal and distal tubular fluid and EV blood samples were collected from rats. End proximal volume reabsorption (PT_{H_2O}) and PAH secretion (PT_{PAH}) were respectively 50 ± 2% (SEM) and 56 ± 6% of the filtered load. Distal tubular PAH was 170 ± 9% of the filtered load, indicating that the proximal convolution secreted 33% and the pars recta 67% of the total PAH secreted by the superficial cortical proximal tubule. The percentages of filtered water reabsorbed into (EV_{H_2O}) and PAH extracted from (EV_{PAH}) EV plasma were 12 ± 4% and 50 ± 5% respectively. The EV_{PAH} was not significantly different from PT_{PAH}, despite the fact that EV_{H_2O} was only 24% of PT_{H_2O} ($p<0.001$). Thus, PAH must be extracted from EV plasma by the pars recta. This results in a preferential reduction of PAH concentration in EV plasma before it reaches the peritubular capillary network. This short-circuiting may be important in determining delivery of these substances to the various segments of the renal tubule.

AMMONIA PARTITIONING BETWEEN GLUTAMINE AND UREA: INTERORGAN CONTROL IN METABOLIC ACIDOSIS. T. C. Welbourne and V. Phromphetcharat, LSU Medical Center, Shreveport, LA.

Metabolic acidosis results in a 5 to 10 fold increase in renal glutamine extraction yet plasma levels are maintained suggesting either an increased turnover or decreased extrarenal utilization. To determine whether extra-renal uptake was altered, male Sprague-Dawley rats were made chronically acidotic by administering NH_4Cl, 1.5% in the drinking solution for at least one week, and arteriovenous, A-V, glutamine, alanine and ammonia concentrations were measured across the kidneys, muscle, intestine and liver. Metabolic acidosis resulted in reduced plasma glutamine levels, 0.48±0.4 vs 0.66±0.10μmole ml^{-1} in controls and a 6 fold rise in renal glutamine uptake, 0.04±0.04 vs 0.25±0.09μmole ml^{-1}. Urinary ammonium excretion increased from 142±58 to 1,970±236μmole day^{-1} $100g^{-1}$ while urea excretion decreased from 2.236±216 to 1,410±307μmole day^{-1} $100g^{-1}$ indicating a shift of precursor nitrogen from ureagenesis to glutamine synthesis. Control A-V glutamine across muscle, -0.11±0.03, intestine 0.12±0.04 and liver 0.17±0.09μmole ml^{-1}, indicate that intestine and liver uptake is balanced by muscle release: renal uptake is not a significant factor. In acidosis, both the kidneys 0.25 ±0.09 and intestine 0.16±0.07 remove glutamine while muscle, -0.18±0.06 and interestingly, the liver, -0.19±0.08μmole ml^{-1} now release glutamine. Consequently glutamine homeostasis appears to be maintained, although at a significantly lower level by a reversal of hepatic uptake to release in acidosis, this reversal results in a shift of nitrogen from ureagenesis to glutamine synthesis.

INSULIN SECRETION FROM ISOLATED ISLETS CELLS OBTAINED FROM UREMIC RATS. José R. Weisinger, Valentina Wallis,* Vivian Gallego,* Carmen Rivas* and Eduardo Coll-García* Departments of Medicine and Physiology. Laboratorio de Investigaciones Clinicas. Universidad Central de Venezuela. Caracas.

Previous work in our laboratory has demonstrated an inhibition of insulin secretion when pancreatic islets were incubated in the presence of serum obtained immediately before a single hemodialysis in chronically hemodialyzed patients.

To further delineate the effect of uremia we incubated isolated islets cells in the presence of glucose (3 mg/ ml) with serum obtained from terminal uremic and nonuremic control subjects.

The values for immunoreactive insulin analyzed in the supernatant were 45.3 ± 24.7 and 260 ± 47.9 microunits/ 5 islets / hour for the uremic and control subjects respectively ($p<0.01$).

At the same time we compared the insulin response to the same ammount of glucose (3 mg/ ml) of islets isolated from acutely uremic (bilateral nephrectomy) rats and sham operated rats.

The values for immunoreactive insulin analyzed in the supernatant were 233.2 ± 77.6 and 279.8 ± 47.1 microunits / 5 islets/ hour for the uremic and control islets respectively (n.s.).

These results suggest that an inhibition of insulin secretion is present in uremia and that it is probably due to a humoral inhibitory factor, since the islets isolated from pancreas of acutely uremic rats responded normally to the glucose challenge.

"REVERSAL" OF THE H^+ PUMP IN THE TURTLE BLADDER FAILS TO INCREASE ATP SYNTHESIS. C. Westenfelder, and J.A.L. Arruda. Univ. of IL, Chicago, IL.

It has been proposed that the H^+ pump in the turtle bladder is a H^+-ATPase. This notion was based on the observation that 1) H^+ transport depends on the availability of ATP and 2) that imposition of an electrochemical gradient greater than the proton motive force leads to pump reversal and ATP synthesis by the H^+-ATPase (when bladders are poisoned with NaCN and iodoacetate, IAA). In order to further confirm the presence of a H^+-ATPase in the turtle bladder, ATP synthesis was measured using two different techniques. First, we measured ATP levels in poisoned bladders using a protocol previously published by others. Poisoned turtle bladders were exposed for 90 min to an adverse electrochemical gradient of 310 mV (mucosa positive). Total ATP levels (firefly Luciferase assay) were not different in 12 poisoned control (3.2±0.9 nmol/mg protein) and 12 poisoned hemibladders exposed to the electrochemical gradient (2.0± 0.5 nmol/mg). Second, $^{32}PO_4$ incorporation into ADP was studied in 15 pairs of identically poisoned bladders. Poisoned control bladders contained 1.2 ±0.3 pmol/mg protein of [γ ^{32}P] -ATP and those exposed to the electrochemical gradient for 5 min contained 0.8±0.2 (NS). These data indicate that an adverse electrochemical gradient does not lead to ATP synthesis in the turtle bladder. The failure to demonstrate ATP synthesis either indicates that the H^+ pump is not a H^+-ATPase or alternatively that an effective electrochemical gradient across the pump cannot be established when bladders are poisoned with NaCN and IAA.

INTERACTION OF PROSTAGLANDINS AND THE RENIN-ALDOSTERONE SYSTEM IN OBESE PATIENTS DURING THE ACUTE PERIOD OF A SUPPLEMENTED FAST. E.T. Zawada, Jr., L.P. Dornfeld, M. Tuck, M. Kirschenbaum, M.H. Maxwell. Univ. of Utah, Salt Lake City, Utah, and U.C.L.A., Sepulveda VA, and Cedars Sinai Medical Centers, Los Angeles, California.

Comparisons were made prior to and three days after starting the use of 320 calories per day as 30 gram carbohydrate, 45 gram protein, and 2 gram of essential fatty acid. Sodium intake was kept constant at 120 mEq/day or less. In 17 patients mean weight fell from 230.8 ± 16.3 to 223.1 ± 15.4 pounds. Urinary sodium (UNaV) decreased significantly from 181.6 ± 22.5 to 69.5 ± 10.7 mEq/day, $p < .001$. Plasma renin activity (PRA) rose significantly from 111.4 ± 14.3 to 320.8 ± 74.8 ng/dl/hr., $p < .02$. Aldosterone levels (ALDO) fell from 16.9 ± 3.1 to 11.3 ± 2.4 ng/dl, and urinary prostaglandin excretion (UPGEV) increased from 796.6 ± 195.6 to 1359.2 ± 267.0 ng/day. In 7 matched patients taking 648 mg aspirin 4 x/day, weight loss (ΔWT) was less due to less change in sodium balance, and there was no significant rise in PRA levels. Conclusions: 1) During the dramatic early ΔWT, UNaV significantly falls reflecting a new lower level of sodium balance; 2) Increased UPGEV accompanies these events but concomitant aspirin only partially reduces ΔWT and UNaV; 3) PRA significantly rose, but the failure of ALDO to rise appropriately appears to be the major factor sustaining the natriuresis.

EFFECT OF DIETARY TAURINE (T) CHANGE ON RENAL TAURINE TRANSPORT. Patti W. Albright, Aaron L. Friedman and Russell W. Chesney*, Univ. of Wisconsin Med. School, Dept. of Pediatrics, Madison, Wisconsin.

The renal adaptation to altered dietary amino acid intake has not been studied. Using isolated renal cortical tubule segments we measured the uptake of T in 8 week old rats under 3 dietary conditions. Diets were high T(HTD), 3%T; normal experimental (NX) and low T, no T, low cysteine methionine (LTD). Urinary T in μM/mg Cr ± SEM were HTD 17.1± 1.5; NX 3.6±1; LTD 0.58 ± .14. Plasma T values were not significantly different amongst the diet groups. Thus LTD led to enhanced urinary T reabsorption and HTD led to diminished reabsorption not secondary to overflow taurinuria. Uptake of 0.01 mMT was measured after 5 minute incubation by isotopic distribution ratio (D.R.± SEM) and are depicted below.

HTD	P	NX	P	LTD
6.08±.9	<.01	10.54±.21	<.001	20.14±2.05

Adaptation develops after 3 days on the diet and is complete within 7-10 days. Michaelis Menton Kinentics revealed a 2-limbed uptake system with no difference in "apparent" Km. However, increased Vmax (μM/ml/ICF/5min) was seen in the LTD group in the high affinity, low capicity system (LTD 2.05; NX 0.92; HTD 0.73). Renal adaptation to dietary T alteration develops within 3-7 days of dietary manipulation and appears to be mediated through an increase in transport sites (increased Vmax) with no change in affinity for T (similar KM).

Renal Physiology

● SPECIFIC INHIBITOR OF THE VASCULAR EFFECT OF EXOGENOUS AND ENDOGENOUS ARGININE VASOPRESSIN (AVP). G. Aisenbrey,* M. Manning,* and R. Schrier. Dept. Med., Univ. Colo. Hlth. Sci. Ctr., Denver, CO and Dept. Biochem., Med. Col. Ohio, Dayton, OH.

In initial studies a bolus of AVP (40 ng/kg) increased mean arterial blood pressure (BP) in the conscious rat before (125 to 150 mmHg, $p<.001$) but not after (128 to 129 mmHg) administration of 1-deaminopenicillamine, 2-(O-methyl) tyrosine AVP [dPTyr(Me)AVP]. No pressor agonist effect of the inhibitor was found as BP was not altered in either water-diuresing (128 to 129 mmHg) or in homozygous Brattleboro rats (110 to 110 mmHg). The AVP analogue did not lower BP during a constant infusion of norepinephrine (NE, 4 μg/kg/min) (149 to 149 mmHg) or angiotensin (0.3 μg/kg/min) (130 to 130 mmHg). The specificity of the analogue was further demonstrated in studies in Brattleboro rats receiving a pressor infusion of exogenous AVP (10 ng/kg/min) which increased BP (112 to 136 mmHg, $p<.001$); the AVP analogue totally reversed this pressor effect (BP 136 to 112 mmHg). A vascular effect of endogenous AVP was demonstrated in rats fluid deprived for 24 hours (plasma AVP 21.6 pg/ml) as BP fell (130 to 118 mmHg, $p<.001$) with the AVP antagonist. This depressor effect of the AVP antagonist was not dependent on the renin-angiotensin system since the same fall in BP (130 to 118 mmHg, $p<.001$) was observed in fluid deprived nephrectomized rats. Thus, dPTyr(Me)AVP is a specific antagonist to the vascular effects of exogenous AVP but not angiotensin or NE. dPTyr(Me)AVP has no inherent agonist pressor effect. A vascular role of endogenous AVP was implicated as the AVP antagonist significantly lowered BP in fluid deprived rats.

● PROXIMAL TUBULE BICARBONATE PERMEABILITY IN THE RAT: EFFECT OF VOLUME EXPANSION AND METABOLIC ALKALOSIS. Robert J. Alpern, Martin G. Cogan, and Floyd C. Rector, Jr., CVRI, Depts. of Med. and Physiol., Univ. of Calif., San Francisco, CA.

Volume expansion is known to increase bicarbonate delivery out of the proximal tubule. It has been postulated to do so by increasing bicarbonate backleak via an increase in bicarbonate permeability. This study was designed to estimate the magnitude of bicarbonate permeability in volume contracted and expanded states. Superficial proximal convoluted tubules of Wistar rats were perfused in vivo at 15 nl/min with a solution containing zero bicarbonate, pH 5, with raffinose added to inhibit volume flux and acetazolamide (0.5mM) added to inhibit acidification. Bicarbonate permeability was calculated from total CO_2 entry as measured by microcalorimetry. There were three experimental groups: 1) Hydropenia (HYD); 2) Isohydric Volume Expansion (VE), 10% body weight Ringer's bicarbonate; 3) Expansion Alkalosis (ALK), 10% body weight isotonic HCO_3^-. The results are reported as mean ± SEM.

	Plasma $[HCO_3^-]$ (mEq/L)	HCO_3^- Permeability ($\times 10^{-5}$ cm/sec)	
HYD	24.6 ± 0.8	2.8 ± 0.3	P<.05
VE	24.1 ± 0.5	4.1 ± 0.4	NS; P<.01
ALK	35.2 ± 0.7	4.1 ± 0.3	

In conclusion: 1) Volume expansion is associated with a 50% increase in bicarbonate permeability. 2) Metabolic alkalosis causes no additional change other than that attributable to volume expansion. 3) Bicarbonate permeability is low, but may be of sufficient magnitude to be one of the determinants of end-proximal bicarbonate concentration and distal delivery.

● DOPAMINE (D) INHIBITS WATER TRANSPORT IN THE TOAD BLADDER: ROLE OF LOCALLY FORMED DOPAMINE. J.A.L. Arruda and S. Sabatini. Univ. of IL, Chicago, IL.

D administration in vivo increases renal excretion of water and electrolytes. It is unclear whether these effects of D are the result of hemodynamic alterations or a direct cellular effect of D. We examined the effect of D on baseline and vasopressin (AVP) stimulated water flow in the toad bladder. D, in concentrations greater than 10^{-6}M, failed to alter baseline water flow but caused a significant inhibition of AVP or cyclic AMP stimulated water flow, (control 130.2±9.6 and D, 10^{-4}M, 104.9±6.1 µl/cm^2/hr $p<0.02$). This effect was not mediated by stimulation of alpha adrenergic, beta adrenergic or cholinergic receptors. The selective antagonist of the dopaminergic receptor, metoclopramide (M), prevented the inhibitory effect of D on water flow indicating this effect of D is mediated through a specific D receptor (D 80.1±7.9 M+D 122.6±14.8 $p<0.025$). L-Dopa, a precursor of D, was also able to inhibit AVP stimulated water flow. L-Dopa could cause this effect either directly or as the result of conversion to D by the presence of a L-Dopa decarboxylase present in the toad bladder. Toad bladder epithelial cells were capable of decarboxylating ^{14}C-L-Dopa as measured by the production of $^{14}CO_2$. The L-Dopa decarboxylase inhibitor, carbidopa (C), prevented this effect. C also prevented the inhibitory effect of L-Dopa on AVP stimulated water flow (L-Dopa 77.2±8.2 C+L-Dopa 103.1±10.5 $p<0.025$). These results indicate that L-Dopa is converted to D by the toad bladder and D inhibits water flow by interacting with a specific D receptor. Since D can be formed in toad bladder it thus can serve as a local modulator of water transport.

● EVIDENCE FOR ACTIN-BINDING PROTEIN (ABP) AND GELSOLIN ACTIVITY IN VASOPRESSIN (VP)-SENSITIVE EPITHELIA Dennis A. Ausiello and John H.Hartwig,*Dept.of Med., Mass. Gen. Hosp., & Harvard Med. School,Boston, MA

The hydroosmotic effect of VP in toad bladder epithelium (TB) may be mediated by actin filaments in the apical cytoplasm. These filaments have been proposed to induce the movement of the transmembrane water channels from cytoplasmic to luminal membranes, a process inhibitable by cytochalasin B. In eukaryotic cells, ABP organizes F-actin into a gel lattice the structure of which is regulated by gelsolin, a Ca^{++}-activated protein that reversibly shortens actin filaments. We have demonstrated that ABP and gelsolin are in the VP-sensitive TB and cultured LLC-PK_1 cells. Peptides which comigrate with purified ABP (270K) and gelsolin (91K) were found by SDS-PAGE of cell extracts. The ABP polypeptides comprised 0.2 and 0.7% and gelsolin, 3.1 and 5.4% of the total protein of TB and LLC-PK_1 cells, respectively. ABP and gelsolin were specifically identified in LLC-PK_1 cells by transfer of these peptides to nitrocellulose sheets and immunological staining with IgG antibodies prepared against macrophage ABP and gelsolin. Similar studies with TB cells demonstrated no cross-reactivity with these mammalian antibodies. Therefore we fractionated TB extracts for gelsolin and ABP activity on a 4% agarose column. TB ABP eluted at the same position as macrophage ABP and had the predicted rigidifying effect on F-actin solutions. A fraction enriched for a 91K peptide demonstrated gelsolin activity, decreasing the viscosity of F-actin solutions in µM but not sub µM free calcium. In conclusion,ABP and gelsolin are present in VP-sensitive cells providing the elements for Ca^{++}-dependent regulation of actin structure. VP could influence this structure by changing Ca^{++} levels.

● VANADATE (V) INHIBITS H^+ SECRETION IN THE TURTLE BLADDER. J.A.L. Arruda, S. Sabatini, C. Westenfelder, (intr. by Franklin Schwartz). Univ. of Illinois, Chicago, Illinois.

V inhibits various ATPases including the proton ATPase of fungal membranes. H^+ secretion in the turtle bladder is thought to be mediated by a proton ATPase. The effect of V on H^+ secretion was investigated in short circuited hemibladders in presence of 1% CO_2 and ouabain. V, added to the serosa, caused a significant inhibition of H^+ secretion (expressed as % of baseline values) (control 100±4.2 V, 10^{-4}, 59.0±7.9 $p<0.001$). The effect was dose dependent and not reversible with 5% CO_2 stimulation. Addition of V to the mucosa failed to alter H^+ secretion. ^{48}V uptake was thirty times greater from the serosa than from the mucosa thus explaining the lack of inhibitory effect with mucosal addition. Since disulfonic stilbenes (e.g. SITS) have been shown to prevent uptake of V we examined the effect of SITS on ^{48}V uptake. SITS failed to prevent both V uptake and the effect of V on H^+ secretion. V inhibited H^+ secretion by decreasing the force of H^+ pump (2.87 ±0.30 to 2.25±0.27 pH units $p<0.02$) without affecting backleak of H^+ or secretion of HCO_3. In presence of mitochondrial inhibition V caused the same inhibitory effect on H^+ secretion. Under these conditions V significantly increased lactate production but did not alter total ATP levels or ATP synthesis as assessed by ^{32}P incorporation. Thus the inhibition of H^+ secretion by V cannot be explained by lack of ATP availability. V inhibits H^+ secretion in the turtle bladder either by interfering directly with the pump (inhibition of proton ATPase) or by preventing energy utilization by the pump.

ADH-INDUCED NATRIURESIS IN HYPOPHYSECTOMIZED DOGS. Robert O. Banks* (intr. by V.E. Pollak), Univ. Cin. Coll of Med., Dept of Physiol. Cincinnati, O.

It is well known that both ADH and oxytocin (OXY) have natriuretic properties. Nonetheless, whether hypophysectomized (HPX) animals can excrete sodium during sodium loading has not been widely investigated. We have evaluated the ability of pentobarbital anesthetized, acutely HPX and sham operated (SO) dogs to excrete an I.V. saline load. Effects of ADH and OXY on electrolyte excretion in expanded HPX dogs were determined. The urine osmolality in 9 HPX dogs was 119 ± 9 (±SE) vs 1145 ± 155 mOsm/L in 6 SO dogs prior to saline. Dogs were expanded with isotonic saline (2 ml/kg-min for 15 min then 0.5 ml/kg-min). Fractional sodium excretion (FENa) was 8.8 ± 1.0, 7.2 ± 0.9, and 8.1 ± 1.1% in SO dogs but only 1.5 ± 0.3, 2.8 ± 0.4 and 3.7 ± 0.5% in HPX dogs after 1, 2, and 3 hrs of expansion, respectively. In another group of 6 HPX dogs infusion of ADH at a dose of only 6 mU/kg primer and 0.1 mU/kg-min during the 2nd hr of expansion resulted, within 1 hr, in FENa values of 8.1 ± 1.1%. Addition of the same amount of oxytocin during the 3rd hr with ADH did not result in a further natriuresis. In a 3rd group of 6 HPX dogs, OXY was infused during the 2nd hr of expansion. After 1 hr FENa was only 2.4 ± 0.4%, a value not significantly different from FENa in untreated expanded HPX dogs. Infusion of ADH into the OXY-treated HPX dogs resulted in a prompt natriuresis (FENa increased to 7.0 ± 0.7% within 1 hr). These data demonstrate that there is an attenuated natriuresis in saline expanded HPX dogs and, compared ot oxytocin, ADH is a more potent natriuretic agent.

DIURETIC EFFECTS ON THICK ASCENDING LIMB Na^+-K^+-ATPase ACTIVITY: STUDIES BY ELECTRON PROBE IN RAT, RABBIT, AND DOG. R. Beeuwkes, J. Shahood*, and S. Rosen. Dept. of Physiology, Harvard Med. Sch. and Dept. of Pathology, Beth Israel Hosp., Boston, MA.

Diuretic agents may act through inhibition of the Na^+-K^+-ATPase system of the thick ascending limb. We have examined the effect of ouabain (O), furosemide (F), mersalyl (M), and vanadate (V) on the ATPase system of this segment using a new electron probe microchemical method which allows measurement of enzyme activity in identified nephron segments (Beeuwkes and Rosen, J. Histochem. Cytochem. 23:828, 1975). This method measures the amount of inorganic phosphate produced by a ouabain sensitive, K^+ dependent phosphatase which is part of the Na^+-K^+-ATPase system. Approximately 27,000 medullary thick ascending limbs were studied in 10 micron tissue sections after incubation in test and control media.

	K_I mM/L (50% Inhibition)			
	O	F	M	V
Rat	3×10^{-4}	10^{-3}	3×10^{-5}	10^{-7}
Rabbit	10^{-5}	2×10^{-3}	3×10^{-5}	5×10^{-8}
Dog	5×10^{-7}	10^{-3}	10^{-5}	10^{-8}

Marked species variation was found only with ouabain, consistent with tissue homogenate studies. The enzyme was relatively insensitive to furosemide but was quite sensitive to the mercurial diuretic. The extreme sensitivity to vanadate ion in all three species supports the possibility that this ion may be a physiological regulator.

INTRACELLULAR ELECTRICAL POTENTIALS IN ISOLATED PERFUSED STRAIGHT PORTIONS (PR) OF RABBIT PROXIMAL TUBULE. Elsa Bello-Reuss. Dept. of Medicine, Jewish Hospital and Dept. of Physiol. and Biophys., Washington University, St. Louis, Missouri.

Cell membrane potentials were measured in PR perfused in vitro with a high Cl-low HCO_3 Ringer, with 3M KCl-filled microelectrodes (of around 45 MΩ).

In 7 tubules, the transtubular potential (V_l) was +2.0 ± 0.6 mV when the bath was a 25 mM HCO_3-Ringer, and the potential across the basolateral membrane (V_b) was -59.9 ± 3.1 mV (range -47.0 to -72.0). Equimolar substitutions of K for Na in the bath resulted in large reductions of V_b. In 7 experiments, K elevation from 5 to 149 mM depolarized reversibly both V_l (to +0.22 ± 0.9), and V_b (to -8.8 ± 3.4 mV). Removal of HCO_3 and CO_2 from the bath at constant pH, depolarized V_l from +2.1 ± 0.1 to +0.4 ± 0.5 mV and V_b depolarized from -64.4 ± 2.7 to -23.7 ± 7.4 mV (n=5). Isomolar replacement of N-methyl-D-glucamine for Na (n=2) caused a -0.8 ± 0.1 mV change of V_l and a -6.5 ± 0.5 mV reduction of V_b. In 5 experiments in which the cells were impaled at room temperature (23-25°C), elevation of the bath temperature to 37°C depolarized the basolateral membrane from -67.2 ± 2.2 to -55.8 ± 1.0 mV.

These studies confirm the feasibility of intracellular potential measurements in isolated perfused segments of rabbit kidney, and suggest that V_b is mainly the result of a K diffusion potential. Basolateral membrane Na permeability (P_{Na}) appears to be low. The effects of HCO_3 removal can indicate a sizable basolateral P_{HCO_3} or effects of intracellular pH changes on basolateral P_K.

POTENTIAL ROLE OF MACULA DENSA CYTOPLASMIC CALCIUM IN THE MEDIATION OF TUBULOGLOMERULAR FEEDBACK RESPONSES. P. Darwin Bell* and L. Gabriel Navar. Univ. of Alabama Med. Ctr., Birmingham, AL 35294.

Since calcium (Ca^{++}) is considered to be an important cellular mediator of many stimulus-response mechanisms, we investigated the possibility that cytoplasmic Ca^{++} participates as an intermediary component involved in the transmission of signals from the macula densa receptor system to the vascular effector elements. To test this hypothesis, a Ca^{++} ionophore (A-23187) which increases membrane permeability to Ca^{++} was used to raise cytoplasmic Ca^{++}. Stop flow pressure (SFP) feedback responses were evaluated in rats during retrograde perfusion from an early distal tubule site with an isotonic electrolyte solution (ES), a hypotonic ES (70 mOsm/kg), and a hypotonic ES containing A-23187 (5×10^{-4} M). All solutions contained 4 mEq/l of Ca^{++}. Control SFP averaged 41 ± .6 mmHg in the absence of perfusion. The decrease in SFP during perfusion (15 nl/min) with isotonic ES averaged 12 ± .9 mmHg (n=9). With hypotonic ES, SFP decreased by 6 ± .8 mmHg (n=13). However, during perfusion with the ionophore containing solution, SFP decreased by 16 ± 1 mmHg (n=17). Upon cessation of perfusion, SFP returned to pre-infusion levels in each series. Thus the presence of A-23187 in the hypotonic perfusate resulted in SFP feedback responses which were greater than those observed with both isotonic and hypotonic ES. These results provide the basis for the hypothesis that cytoplasmic Ca^{++} within the macula densa receptor cells participates in the mediation of tubuloglomerular feedback responses.

EFFECT OF AGING ON EXTRARENAL POTASSIUM ADAPTATION. HH Bengele, ER McNamara*, and EA Alexander. Thorndike Mem. Lab.,Renal Section,Boston City Hospital, Depts. Med. & Physiol.,Boston Univ.School Med., Boston, Mass.

Potassium (K) translocation into cells and renal K excretion are important defenses against hyperkalemia and both are enhanced after chronic high-K diet (K adaptation). We recently reported that aging impairs renal K adaptation in rats. To examine the effect of aging on extrarenal K adaptation 24 young (Y,3 mon.) and 24 aged (A,21 mon.) rats ate a regular (0.28 meq/g) or high (2.0 meq/g) K diet for 2 weeks. After anesthesia and acute bilateral nephrectomy, half the rats in each diet group served as controls while the rest received 3 mM KCl equal to 2.5 mM/Kg body weight intraperitoneally. Plasma K was measured 90 minutes after K loading. Results are mean ± SEM.

	Regular Diet		High-K Diet	
	Y	A	Y	A
Control	3.72 ±.09	3.68 ±.10	3.60 ±.08	3.76 ±.06
KCL	5.28 ±.16	5.68 ±.33	4.75 ±.12	5.97 ±.30

The significant increase in plasma K was similar in Y and A on a regular diet. With high-K diet the increment in plasma K was significantly blunted ($P < .01$) in Y but not A. Plasma aldosterone increased similarly with K feeding 9 ± 0.2 to 141 ± 30 Y and 10 ± 2 to 128 ± 27 A, ng/dl.

We conclude that A does not affect cellular K uptake on a regular diet but A significantly impairs extrarenal K adaptation. This defect is not dependent upon aldosterone secretion.

RELATIONSHIP BETWEEN NA TRANSPORT AND TIGHT JUNCTIONAL PERMEABILITY IN NECTURUS GALLBLADDER. C. Bentzel, B. Hainau,* S. Ho,* S. Myers* and M. Martinez.* Dept. Medicine, VA Medical Center, Buffalo, NY 14215.

Agents active against submembranous microfilaments can reversibly increase tight junctional permeability in the leaky epithelium, Necturus gallbladder (GB). GBs mounted in chambers and bathed in amphibian NaCl Ringers (NaR) have an average transepithelial resistance (TR) of 187 Ω cm^2, PD = - 0.1±0.1 mV (lumen negative) and a mucosa to serosa (M to S) fluid transport of 5 to 10 µl/hr. The plant cytokinin, kinetin (0.4 mM), added to the mucosal bath reversibly increases resistance by an average of 17.3%, PD by 0.22 mV and M to S fluid transport by 13%. Gallbladders bathed in either Na_2SO_4 Ringers or treated with ouabain have a 17% and 11% lower TR, respectively, 0 PD or measurable M to S fluid transport. By electronmicroscopy, intercellular spaces are collapsed. Kinetin (0.4 mM) is 2-fold more active in the SO_4 bathed GB. Kinetin tested first in NaR and then after addition of ouabain, 10^{-8} to 10^{-5}M(serosal side) is 1.8 times more active. In the nontransporting GB, raising the serosal bath outflow hydrostatic pressure, thereby dilating intercellular spaces, significantly inhibits the action of kinetin. This effect is reversible. Reorganization of the junctional strand meshwork, as revealed by freeze fracture correlate with changes in TR.

We conclude that transcellular solute transport and transjunctional ionic flux might be interrelated via pressure changes in the intercellular space.

PERITUBULAR PROTEIN REMOVAL SPECIFICALLY INHIBITS NACL TRANSPORT. C.A. Berry and M.G. Cogan. Univ. of California, San Francisco, Departments of Physiology, Medicine, and CVRI, San Francisco, Calif.

The effect of removal of peritubular protein on the reabsorption of various solutes and water was examined in isolated perfused rabbit proximal convoluted tubules (PCT). In 22 PCT perfused with ultrafiltrate (UF) and bathed in serum, volume absorption (Jv) and potential difference (PD) were 1.44 nl/mm min and -3.6 mV. When these same PCT were bathed in a protein-free UF, Jv was reduced 38% without a change in PD. Simultaneous measurements of total CO2 net flux (JTCO2) and glucose efflux (JG) showed that less than 2% of the decrease in Jv could be accounted for by a reduction in JG and JTCO2, suggesting an effect on NaCl transport (JNaCl). Therefore, in 8 PCT JNACl was measured in addition to PD, Jv, JG and JTCO2. Total solute transport decreased 202 ± 38 posm/mm min. JG decreased slightly (9 ± 4 posm/mm min); NaHCO3 transport decreased insignificantly (9 ± 7 posm/mm min); but JNaCl decreased markedly (161 ± 36 posm/mm min). 80% of the decrease in Jv could therefore be accounted for by a decrease in JNaCl. In 13 PCT perfused with NaCl solutions, a comparable decrease in Jv and JNaCl was observed when peritubular protein was removed without an increase in JTCO2 backleak.

Removal of peritubular protein inhibits Jv and JNaCl. The failure to inhibit JG and JTCO2, known sodium-coupled transport processes, indicates that protein removal does not primarily affect Na-K ATPase pump system. Since PD and JTCO2 backleak were not influenced, it is unlikely that protein removal increased the permeability of the paracellular pathway. We conclude that protein removal specifically inhibits the flow of a NaCl solution across either junctional complexes or the lateral cell membranes of intracellular channels.

EFFECT OF CHRONIC CONVERTING ENZYME INHIBITION ON WATER METABOLISM IN THE RAT. T. Berl and M. Ellis.* Dept. Med., Univ. Colo. Hlth. Sci. Ctr., Denver, CO.

Angiotensin II has been suggested to stimulate thirst and arginine vasopressin (AVP) release. Studies were therefore undertaken in the conscious rat to examine the effect of captopril (Capt) on thirst, AVP release and renal concentration. Administration of Capt (30 mg/kg tid, n=12) was associated with a persistent increase in daily water intake ($p<.001$), increased urine flow (V, $p<.005$) and decreased urinary osmolality (Uosm, $p<.01$) when compared to pairfed controls (C, n= 13). Fluid deprivation after 7 days on Capt demonstrated a lower maximal Uosm (1763±83 in Capt vs 2470±77 mOsm/kg H_2O in C, $p<.001$). This defect was not due to suppressed release of endogenous AVP (7.90±1.21 in Capt vs 6.14±0.94 pg/ml in C) nor was it corrected by exogenous AVP. The nephrogenic diabetes insipidus was associated with a decrease in papillary tonicity (1271±58 in Capt vs 1540±49 mOsm/kg H_2O in C, $p<.005$). The possibility that the concentrating defect is a consequence of a primary increase in water intake was then studied. Experiments were repeated in 12 rats receiving Capt whose fluid intake was matched to C. These rats had no increase in daily V, in maximal Uosm (2466±134 mOsm/kg H_2O) or in papillary tonicity (1466±114 mOsm/kg H_2O). The present study therefore demonstrates that chronic Capt administration causes polyuria, polydipsia and nephrogenic diabetes insipidus. The latter defect is entirely due to stimulation of thirst with an increase in water intake. The effect of Capt to stimulate thirst may be due to bradykinin or to some as yet unidentified action of the drug.

EFFECTS OF BATH POTASSIUM AND PH ON INTRACELLULAR POTASSIUM ACTIVITY IN RABBIT PROXIMAL STRAIGHT TUBULE. B. Biagi*, M. Sohtell*, G. Giebisch. (intr. by R.W. Berliner), Yale Univ. Med. School, Dept. Physiology, New Haven, CT.

Double barreled potassium-ion selective microelectrodes were used to measure basolateral membrane potential (V_{BL}) and intracellular potassium activity (A_K) in isolated perfused superficial proximal straight tubules (sPST) of rabbit kidney.

In thirteen sPST the mean ± SE (N=cells) value of V_{BL} was -37.8±2.49(20)mV and A_K was 48.6±2.27mM (20). Calculated Nernst equilibrium potential for potassium (E_K) was -67.9±1.27(20)mV. Bath perfusion with low K solution (0.1mM) resulted in a decrease in V_{BL}=-12.2±1.21(19)mV and A_K=11.3±1.29(19) 10^{-3}mM. Bath ouabain (10^{-3}M) resulted in similar changes in V_{BL} and A_K. High K bath perfusion (14.6mM) following low K solution resulted in a transient state where V_{BL} was more negative than E_K by about 35mV.

Lowering bath pH to 6.7 by reducing bicarbonate concentration produced a rapid (<1 min) and sustained depolarization of V_{BL} (ΔV_{BL}=39.9±1.77(11)mV) as measured with conventional microelectrodes. Barium chloride (0.5mM) added to the control bath solution resulted in a similar time course of depolarization with ΔV_{BL}=16.3±0.71(6)mV. In both cases intracellular potassium activity measured with double-barreled electrodes showed little or no change during the depolarizations of V_{BL}.

It is concluded 1) that intracellular potassium is actively accumulated in sPST primarily by the Na-K pump which is electrogenic in a K depleted cell and 2) that the mechanism for V_{BL} depolarization by low pH and barium is a decrease in relative potassium permeability of the basolateral membrane.

INTRACELLULAR K^+ AND NA^+ CONCENTRATIONS AND WATER SPACE MEASUREMENTS IN ISOLATED PROXIMAL CONVOLUTED TUBULES (PCT). R. C. Blantz, D. Tsiakiris,* K. Hierholzer*. Univ. of Calif., San Diego, La Jolla, CA and Free Univ., Berlin, Germany.

Intracellular Na^+(Na^+_i) and K^+(K^+_i) was defined in PCT, dissected at 4°C with collapsed lumen, from the total Na^+ and K^+ content of PCT measured on a Hampel microflamephotometer and from total H_2O (TH_2O) and extracellular volume (ECV) measurements as determined from equilibration with ^3H_2O and ^{14}C PEG and simultaneous counting. 200 tubules in 26 rabbits were dissected and evaluated 3 to 60 minutes after sacrifice and equilibrated in 4 separate solutions: 1) Control (C)-inert oil, 2) artificial high Na^+ serum (NaS), 3) artificial high K^+ (and Mg^{++}) serum (KS) and 4) normal biologic serum (BS).

	Cell volume (nl/mm/kg BW)	ECV/ TH_2O	K^+_i mM/l	Na^+_i mM/l	K^+_i/Na^+_i
C	(0.44)	(0.36)	122±2	64±13	2.1±0.4
NaS	0.44±0.04	0.36±0.03	41±13†	69±11	0.6±0.1†
KS	0.54±0.04*	0.25±0.04*	82±9†*	35±8*	2.7±0.8
BS	0.51±0.05	0.24±0.04*	31±5†	151±18†*	0.3±0.1†

(†p>0.05 when compared to C(†) or NaS(*)).

The time course of changes K^+_i and Na^+_i was evaluated in the various solutions, and changes in K^+ were rapid within 3-7 minutes with only minimal decay in K^+_i from 7-60 minutes. Conc: 1) PCT cell K^+ permeability is very high, reaching equilibrium in absence of pump activity in 3-7 minutes, 2) total Na^+_i and K^+_i is lower in PCT dissected in either artificial sera, 3) loss of K^+_i can be prevented by dissection in high K^+ serum and 4) in absence of pump activity a 9-fold chemical K^+ gradient (cell/ECV) persists which suggests that other factors affect the distribution of K^+.

● BICARBONATE SECRETION BY ISOLATED PERFUSED RABBIT CORTICAL COLLECTING DUCTS. J. Boyer* and M. Burg, NHLBI, NIH, Bethesda, MD

To study the control of bicarbonate secretion, we measured HCO_3 transport rate from HCO_3 concentration differences (microcalorimeter) and fluid absorption rate. In confirmation of previous work, when ducts from rabbits given $NaHCO_3$ on the day before the experiment were perfused and bathed with plasma ultrafiltrate-like solutions that contained 25mM HCO_3, they secreted HCO_3, and, when the ducts were from NH_4Cl-treated rabbits, they absorbed HCO_3. To measure HCO_3 secretion directly, independent of reabsorption, we perfused with HCO_3-free solution while there was 25mM HCO_3 in the bath. Under those conditions, ducts from $NaHCO_3$-treated rabbits secreted HCO_3, but ducts from NH_4Cl-treated rabbits did not, even when 10^{-3}M amiloride was added to the perfusate in order to inhibit any possible reabsorption of the secreted HCO_3. Replacement of Cl in the perfusate by SO_4 inhibited the secretion of HCO_3 into ducts from $NaHCO_3$-rabbits, when the perfusate was HCO_3-free, and converted secretion into absorption when the perfusate contained 25mM HCO_3. SO_4 did not increase the HCO_3 absorption which was present after NH_4Cl-treatment. We conclude: 1) Secretion and absorption are simultaneous, but separate processes. 2) NH_4Cl versus $NaHCO_3$ treatment inhibits secretion. 3) SO_4 replacement of Cl in the perfusate also inhibits secretion. 4) The SO_4 inhibition of HCO_3 secretion should result in increased urinary acidification, which was previously observed following systemic SO_4 infusion in vivo.

● INTRACELLULAR pH REGULATION IN SALAMANDER RENAL PROXIMAL TUBULE. Walter F. Boron* and Emile L. Boulpaep. Dept. Physiol., Yale Univ. School of Medicine, New Haven, CT.

We have used pH- and Na-sensitive glass and Cl^--sensitive liquid ion exchange microelectrodes to study mechanisms of H^+ and HCO_3^- transport in cells of the salamander proximal tubule. Intracellular pH, pH_i, was lowered by 0.3-0.4 in HCO_3^--free Ringer by applying and then removing NH_4Cl; pH_i recovers from the acid load (representing active H^+ extrusion) with an exponential time course. The recovery was not inhibited by stilbenes or Cl^- removal, nor accompanied by changes of intracellular Cl^- activity, a^{Cl}_i, but was attended by a transient rise of a^{Na}_i, and was blocked by removal of Na^+ from bath and lumen, b&ℓ. Returning Na^+ to b or ℓ caused pH_i recovery. Amiloride (2mM) inhibited the recovery ∿50% when present in b or ℓ, and ∿75% when in both. The data indicate that Na-H exchangers exist on both basolateral and luminal membranes.

When tubules were bathed in HCO_3^--Ringer, lowering pH_b from 7.5 to 6.8 (constant CO_2 tension) caused a rapid, reversible fall in pH_i by 0.3-0.4, whereas lowering pH_ℓ had no effect. In HCO_3^--free Ringer, reducing pH_b or pH_ℓ had little effect. These HCO_3^--dependent pH_i changes were largely blocked by SITS, but not by Cl^- removal, nor were they accompanied by changes of a^{Cl}_i. The data suggest that permeability to HCO_3^- or a related species is limited to the basolateral membrane (blm). We propose that acid secretion is initiated by HCO_3^- efflux across the blm, which lowers pH_i and thereby stimulates b and ℓ Na-H exchange. The latter exchange constitutes net acid secretion.

DETERMINANTS OF RENAL PROSTAGLANDIN PRODUCTION: PCO_2 AND pH. Daniel W. Brash,* Alan H.Stephenson,* and Andrew J. Lonigro. VA Med. Ctr. and St. Louis Univ. School of Med., Dept. of Med., St. Louis, Missouri.

Alterations in rates of renal prostaglandin(PG) synthesis were reported to affect renal blood flow (RBF), its distribution and renal salt and water excretion. Although several interventions are known to affect renal PGs, a comprehensive description of the determinants of their synthesis awaits further investigation. To assess effects of altered acid-base status on renal PGs in anesthetized dogs, aortic and renal venous samples for radioimmunoassay of PGE_2 and $PGF_{2\alpha}$ were obtained prior to and during respiratory alkalosis (hyperventilation) respiratory acidosis (ventilation with 20% O_2 and 3% CO_2), metabolic alkalosis ($NaHCO_3$ infusion) and metabolic acidosis (0.3 M HCl infusion). Respiratory alkalosis (PCO_2:22 ± 1 mmHg, pH 7.468 ± 0.009) increased renal venous PGE_2 and $PGF_{2\alpha}$ by 47 ± 16 ($P < 0.05$) and 100 ± 37 pg/ml ($P < 0.05$) from controls of 51 ± 9 and 109 ± 18 pg/ml, respectively; whereas, metabolic alkalosis produced no change. Neither intervention affected arterial concentrations of PGE_2 or $PGF_{2\alpha}$. On the other hand, metabolic acidosis (PCO_2:33 ± 3 mmHg, pH: 7.217 ± 0.011) produced significant increases in renal venous $PGF_{2\alpha}$ but not PGE_2, and no change in their arterial concentrations. None of these interventions affected RBF or mean arterial blood pressure. These results suggest that alterations in pH and/or carbon dioxide tension may be important determinants of renal PGE_2 and $PGF_{2\alpha}$ production. The consequences of these alterations may be resolved in terms of re-distribution of intrarenal blood flow, or alterations of renal excretory events.

EXCHANGE TRANSPORT OF SULFATE IN RABBIT PROXIMAL TUBULES. P.C. Brazy and V.W. Dennis, Durham VA and Duke University Medical Centers, Durham, NC.

The renal mechanisms of sulfate transport are uncertain. While tubular reabsorption is the dominant process, the coexistence of tubular secretion has been suggested. In this study, we examine both absorptive and secretory fluxes of sulfate to clarify the mechanisms of transport. Proximal convoluted tubules from rabbit kidney were perfused in vitro with physiological fluids and bathed in the same fluid plus albumin. Sulfate fluxes were measured at different sulfate concentrations with radioisotopic techniques. Both unidirectional fluxes saturated with increases in sulfate concentration. Kinetic analyses of these data indicate maximum transport rates of 5.77±0.88 and 5.42±0.48 pmol/mm·min for absorptive and secretory fluxes, respectively. The apparent Km of the absorptive flux was less than that for the secretory flux (0.55±0.26 versus 1.76±0.41 mM, $p<0.01$). Sulfate absorption is thus favored at physiological concentrations. Additional studies showed that the unidirectional fluxes are interdependent such that an increase in the perfusate concentration of sulfate from 0.2 to 1.0 mM stimulated sulfate secretion (1.39±0.26 to 3.44±0.55 pmol/mm· min, $p<0.01$). Similar increases in the bath sulfate concentration stimulated sulfate absorption from 2.23±0.53 to 3.68±0.78 pmol/mm·min ($p<0.02$). This interdependence defines an exchange transport mechanism. Thus, sulfate transport in the proximal convoluted tubule occurs via carrier-mediated processes for both absorption and secretion and these processes interact via an anion exchange mechanism.

CORRELATION OF URINARY PROSTAGLANDINS (PG) WITH VOLUME RATHER THAN SODIUM EXCRETION IN MAN. D. Craig Brater, Sming Kaojarern,* Polavat Chennavasin,* and William B. Campbell*. Univ. of Texas Health Science Center, Dept. of Pharmacology, Dallas, Texas.

We analyzed urinary PGE_2 excretion during various conditions of volume and Na excretion in 8 normal subjects. All subjects underwent water loading alone and plus 40 mg of furosemide IV, ad lib fluid intake alone and plus furosemide, and each of the preceeding after pretreatment with indomethacin. Subjects ingested a pre-study diet containing 150 mEq Na and 60-80 mEq K per day. In the ad lib intake studies, fluid losses were replaced intravenously. PGE_2 was measured by radioimmunoassay. During the parallel increases in Na and volume excretion after furosemide administration, urinary PGE_2 correlated closely with Na excretion ($y=1.03x-0.28$; $r=0.940$; $p<0.0001$). Indomethacin pretreatment did not modify this relationship. In the absence of the diuretic, urine volume varied over a wide range (0.5-15 ml/min) with little change in sodium excretion. Again, urinary PGE_2 correlated with urinary Na ($y=0.12x+0.05$; $r=0.879$; $p<0.0002$). However, the correlation differed markedly from that observed in the studies with furosemide. Expressing urinary PGE_2 as a function of urine volume for all studies resulted in a highly significant correlation ($y=10.7x-0.70$; $r=0.975$; $p<0.0001$). Multiple and step-wise regression analyses confirmed that the correlation with urinary PGE_2 could be totally accounted for by urine volume. Conclusion: *In the conditions of this study in man, urinary PGE_2 is a correlate of urine volume rather than sodium excretion.*

● EFFECT OF VASOPRESSIN ON INTRACELLULAR pH IN THE TOAD URINARY BLADDER. A.S. Brem , J. Tetreault*, D. Clark* and A.G. Taylor . Brown Univ., Providence RI and Cornell Univ. Med. Coll., New York, NY.

Acidification of the serosal bathing medium has been shown to inhibit vasopressin (VP) induced water movement in the toad bladder. To directly assess the intracellular response to serosal acidification, measurements of intracellular pH (pH_i) were carried out using the DMO method. Serosal pH (pH_s) was varied utilizing a standard amphibian Ringers with 2.4 mM HCO_3 and gassing each experimental series with a different CO_2-O_2 mixture. Over the pH range 6.5 to 7.5, the pH_i was significantly more alkaline than the corresponding pH_s by as much as 0.405 ± 0.022 pH units ($n=7$, $p<0.001$) at pH_s 6.5. However, no difference was apparent at pH_s 8.3. After exposure to VP (20 mU/ml) in the pH_s range 6.5 to 7.5, pH_i was further increased relative to controls. A maximum difference of 0.11 ± 0.041 pH units was seen at pH_s 7.1 ($n=17$, $p<0.02$). Since low serosal Na inhibits VP induced water movement, the effect of 20 mM Na-choline Ringers on pH_i was examined over the pH_s range 6.8 to 8.3. While remaining alkaline with respect to the serosal medium, the pH_i was lower than paired controls at pH_s 7.5 and below. Low serosal Na however had no effect on pH_i at pH_s 8.3. The effect of low Na on pH_i was observed even in the presence of VP. These findings are consistent with the view that 1) under acidic conditions VP can raise intracellular pH, and 2) the alkalinization process appears to be dependent on serosal Na.

THE ROLE OF NaCl IN GENERATING OSMOTIC FORCE ACROSS A "LOOSE" EPITHELIUM. E.H. Bresler and K.T. Neilsen.* Research Service, VA Medical Center and Tulane School of Medicine, New Orleans, Louisiana.

Absorptive pressures generated across the rat jejunal membrane are measured in vivo by introducing the multiperforated half of a fluid filled polyethylene catheter into the lunen of a segment of jejunum. The catheter is tied into place so that the perforated end is isolated and sealed in the jejunal segment and the non-perforated end extending outside is connected to a Statham transducer. As fluid is reabsorbed from this quasi-rigid system subatmospheric (negative) pressure is generated (Bresler, et al, A.J.P. to be published). To prevent herniation of gut into perforations either filter paper (F.P.) or a tubular dialysis membrane with molecular weight cut off of 12-14000 (D.M.) covering is required. The mean negative pressures measured with the two coverings differed markedly: 71 mm Hg (N=11, S.D. 28) for F.P. and 410 mm Hg (N=11, S.D. 63) for D.M. Since F.P. has a reflection coefficient (σ) of zero for all solutes, measurements made with it reflect the absorptive (osmotic) force generated across the intestinal membrane itself. The higher pressures recorded using D.M. indicate that solutes responsible for absorptive force have higher σ's across it than the gut membrane. Since the σ for NaCl is near zero for D.M. the osmotic force is not due to a concentration difference of NaCl but rather to that of solutes of larger molecular radii. Moreover they have a lower aggregate σ across the major convective pathway of gut epithelium (paracellular shunt?) than across D.M. This implies that σ for NaCl across the major epithelial pathway is near zero. We conclude that the absorptive forces generated are not related to NaCl but to larger solutes.

ENERGY DEPENDENT BINDING OF ANGIOTENSIN II (ANG II) TO RAT RENAL BRUSH BORDER MEMBRANES (BBM). G.P. Brown,* and J.G. Douglas* (intr. by I. Dresner). Case Western Reserve University, Depts. of Medicine and Pediatrics, Cleveland, Ohio.

Since Ang II affects renal tubular electrolyte transport we have studied the influence of transmembrane potential differences of renal BBM vesicles on Ang II binding. Radioreceptor assays were performed using ^{125}I-Ang II. Results are reported as mean $\pm$ SD. Specificity of binding was confirmed with the use of Ang II analogs. Scatchard analyses indicated the presence of a single class of high affinity sites (K_d=5$\pm$.6nM, n=4). Receptor concentration was 502$\pm$45 fm/mg protein with an ionic concentration gradient across the vesicular membranes (extravesicular>intravesicular) contrasted with 124$\pm$22, n=14, without a gradient. NaCl, KCl, LiCl and $MgCl_2$ gradients enhanced binding, suggesting an anion effect on binding. To assess this, we compared the effects of Cl and SO_4 gradients on binding since gradients of the permeant anion, Cl, would result initially in a relatively more electronegative intravesicular space than similar gradients of the poorly permeable anion, SO_4. Initial binding was enhanced (n=4, $p<.05$) in the presence of $MgCl_2$(25mM) and NaCl (100mM) gradients as compared to similar SO_4 gradients. Also, binding in the presence of K_2SO_4 or KCl gradients was reduced by increasing membrane K conductance with valinomycin. These studies provide evidence for Ang II receptor regulation by energy inherent in transmembrane potential differences and imply that a Cl potential across the renal brush border membrane may play an important role in Ang II binding.

FEEDBACK RESPONSES DURING ORTHOGRADE PERFUSION (OP) DEPEND UPON DISTAL CL CONCENTRATION ($[CL]_D$) EVEN WITH INITIALLY CL-FREE SOLUTIONS. Josephine Briggs, Gisela Schubert*, and Jürgen Schnermann*. Dept. of Physiology, Univ. of Munich, Munich, W-Germany.

Microperfusion of the loop of Henle from the distal tubule in a retrograde direction(RP) results in a decrease in early proximal flow rate (ΔV_{EP}) only when perfusion fluid contains Cl or Br. However during OP responses have been elicited with Cl-free solutions. In order to reevaluate causes of this discrepancy, the feedback response(ΔV_{EP}), distal flow rate (V_D) and distal Cl concentration were measured during OP with low Cl and no Cl solutions:

	OP rate (nl/min)	V_D (nl/min)	$[Cl]_D$ (mM)	ΔV_{EP} (nl/min)
mannitol	10	15.0±1.2	41.0±2.1	-5.1±0.7
(300 mOsm)	20	23.5±2.2	32.5±3.0	-4.6±0.9
	40	46.8±4.6	30.6±1.2	-1.4±0.6
mannitol+30mM	20	21.3±0.9	44.3±1.7	-8.2±1.0
NaCl (300mOsm)	40	41.1±1.6	45.5±1.6	-11.8±1.4
NaIsethionate	20	15.8±1.1	23.8±3.0	-3.3±0.9
(140 mM)	40	34.7±1.7	20.6±1.2	-2.9±0.9

The linear regression relation calculated from individual OP data, $\Delta V_{EP}=5.5-.3[Cl]_D$, does not differ significantly from that determined from previous RP measurements for the $[Cl]_D$ range 20 to 60 mM, $\Delta V_{EP}=3.6-.27[Cl]_D$. Conclusions: 1) The feedback response seen during OP with low Cl or no Cl solutions can be explained by Cl entry into perfusion fluid; 2) the OP technique alone does not permit characterization of the feedback signal because of perfusate composition changes; 3)when V_D is greater than 15 nl/min, the relationship between $[Cl]_D$ and the feedback response is the same during OP and RP; at lower V_D, $[Cl]_D$ may not reflect [Cl] at the macula densa.

ROLE OF DEEP NEPHRONS (DN) AND THE COLLECTING DUCT (CD) IN URINE ACIDIFICATION. J. Buerkert, D. Martin,* D. Trigg,* and S. Chambless*. VA Hospital, Wash. Univ. Med. Serv., St. Louis, Mo.

Urine acidification is thought to involve CD entrapment of NH_3 delivered to the medulla in ionic form by the loop of Henle where, because pH increases, it is converted to NH_3 which then leaves the lumen and enters the CD. To test this hypothesis, papillary and surface micropuncture was performed in the rat. pH was measured at proximal (CDprox) and tip CD sites with micro pH electrodes. $HCO3^-$ and NH_4+ were measured in fluid from these sites, at end proximal tubule sites (EPT) of surface and at the bend of the loop of Henle (BLH) of DN. The NH_4+ content of fluid from the BLH was 14±2 mEq/L as compared to 3±0.4 mEq/L, at EPT ($p<.001$). Delivery of NH_4+ to the BLH was 86±10 pEq/min/g K.W., twice the amount at EPT (43±6, $p<.001$) implying continued entry of NH_4+ beyond the EPT. Fractional delivery (FD) to the BLH was greater ($p<.001$)than to CDtip (1304±235 vs 731±69%, $p<.001$) suggesting that NH_4+ may be carried away from the medulla. $HCO3^-$ content near the BLH was greater than at EPT (16±2 vs 10±2% mEq/L, $p<.05$). This increase in $HCO3^-$ content could increase luminal pH and cause the reduction of NH_4+. The pH was 5.92±.14 at CDprox and 5.33±.16 at the CDtip. This increase in H^+ content was only partially a result of water extraction indicating H^+ secretion along this segment. NH_4+ content rose between base and tip sites (126±20 and 157±26 mEq/L respectively), but was accounted for by water extraction. Thus, while conditions found may allow ammonia to diffuse out of the loop and into the CD, the site of entry is not located along the terminal segment of the CD.

EFFECT OF DITHIOTHREITOL (DTT) ON VASOPRESSIN-SENSITIVE ADENYLATE CYCLASE (AVP·AC) IN B. Marinus, D.E. Butkus and J.H. Schwartz, Walter Reed Army Institute of Research and Boston University School of Medicine, Washington, D.C. and Boston, Mass.

We have previously demonstrated that the reducing agent DTT inhibits the hydrosomotic and natriferic responses to AVP at a site proximal to generation of cAMP and that these inhibitory effects can be partially reversed by oxidizing agents (K.I. 16:869A, 1979) and by GppNHp.

To further investigate the mechanism of the inhibition of DTT on AVP responsiveness we studied the effect of DTT on AVP·AC in toad bladder membrane vesicles. DTT, 1.0 - 50.0 x 10^{-4}M produced dose dependent inhibition of AVP·AC at AVP 10^{-7} - 10^{-5}M, but did not affect the stimulatory effect of 10^{-2}M NaF or GppNHp (10^{-5}M). GppNHp (10^{-4}M) increased the AC response to 2.7 x 10^{-7}M but not to 2.7 x 10^{-6}M AVP. Neither the stimulatory effect of GppNHp on AVP·AC nor the maximum response to AVP plus GppNHp were significantly inhibited by 2 x 10^{-3}M DTT.

Pre-incubation of membranes in 10^{-3}M DTT followed by washing in DTT-free buffer prior to initiation of the reaction (final dilution ∿ 200:1) resulted in persistant inhibition of the response to AVP. At 2.7 x 10^{-6}M AVP the response was inhibited by 47% when DTT was present in the incubation medium and by 29% when exposed membranes had been washed free of DTT.

These findings are consistent with our previously noted physiologic observations and suggest that DTT inhibits the response to AVP at or proximal to the GppNHp stimulatable site of AC and that the effect is not through inactivation of AVP.

SODIUM CALCIUM EXCHANGE IN THE BASOLATERAL MEMBRANE OF THE TOAD BLADDER. H.S.Chase,Jr. and Q. Al-Awqati. Columbia University, New York, N.Y. 10032

We have previously demonstrated that luminal sodium permeability of the toad bladder is decreased by an increase in cell calcium as well as by a reduction of the trans-serosal sodium gradient. Since this latter effect is dependent upon the presence of serosal calcium, these results suggest the existence of a Na-Ca exchanger in the basolateral membrane.

We purified basolateral membranes by differential and sucrose density gradient centrifugation. The isolated membranes had a nine-fold enrichment of K-activated pNppase, were vesicular on EM and contained an osmotically active space. Vesicles were loaded with NaCl (160mM), MOPS (20mM) and diluted in either NaCl-MOPS or choline Cl-MOPS containing Ca^{45}. An outward directed Na gradient induced calcium uptake (J_{Ca}) of 4(nmol/mg protein) at five minutes, compared to 2 in the absence of a Na gradient. A23187 rapidly discharged the accumulated calcium suggesting that J_{Ca} represented trans-membrane Ca transport. The increase in J_{Ca} was not the result of a Na diffusion potential, as demonstrated by simultaneous measurement of the membrane potential (with the lipophilic cation TPP+) and J_{Ca}. Kinetics of Na dependent J_{Ca} using initial rates (9sec), showed that the Vmax was reduced in the presence of outside Na while the Km was unchanged (0.18-0.22mM).

Estimates of cell Na and Ca activities and the potential across individual cell borders suggest that changes in luminal Na will change the driving force for the flux of Ca through the Na-Ca exchanger. Ca transport via this mechanism might play a regulatory role for Na transport across the epithelium.

EFFECT OF MERCURIC CHLORIDE ($HgCl_2$) AND URANYL NITRATE (UN) ON ULTRAFILTRATION COEFFICIENT (K_f) IN ISOLATED GLOMERULI. R. Cachia*, V.J. Savin*, R.V. Patak, S.M. Ridge*. University of Kansas Medical Center, Kansas City, Kansas.

The nephrotoxic effect of UN involves glomerular as well as tubular functional and structural changes. Documented abnormalities include decreased K_f and loss of endothelial cell fenestrated area. Using a technique for measuring K_f in isolated glomeruli in vitro (Kid Int 12:572, 1977), we have studied the effects of high and low dose UN (5 or 25 mg/kg) and $HgCl_2$ (4 or 10 mg/kg) in rats. UN or $HgCl_2$ was given 24 or 48 hours prior to overnight urine collection for C_{cr}. Kidneys were removed, glomeruli isolated for K_f determination and tissue fixed for histology. All rats developed renal insufficiency with elevated S_{cr} and decreased C_{cr}. Light and transmission electron microscopy showed changes of tubular necrosis. Scanning electron microscopy showed loss of endothelial fenestrae in each group except low dose $HgCl_2$. K_f was significantly decreased from control (5.9 ± 0.4) in low and high dose UN and high dose $HgCl_2$ (3.1 ± 1.2, 3.2, and 3.6 ± 0.01 nl/min·Hg respectively $p < .01$). In contrast, K_f was normal in low dose $HgCl_2$ (5.7 ± 0.5). Thus, renal insufficiency is associated with diminished K_f in both UN and high dose $HgCl_2$ nephrotoxicity. However, altered C_{cr} in low dose $HgCl_2$ is independent of K_f and may be related to hemodynamic changes or tubular backleak of ultrafiltrate. In these studies, low K_f occurred in association with loss of endothelial cell fenestrae suggesting that the area of fenestrae may be a determinant of glomerular hydraulic conductivity.

THE BASIS FOR HETEROGENEITY OF URATE TRANSPORT IN RABBIT PROXIMAL TUBULES. A. Shimomura*, A. Chonko, and J. Grantham. University of Kansas Health Science Center, Kansas City, Kansas.

Unidirectional fluxes of ^{14}C-urate from bath to lumen and from lumen to bath were measured in isolated perfused rabbit proximal tubules (S_1, S_2, S_3 segments). The absorption of urate from the perfusate was small in magnitude and insensitive to alteration by luminal probenecid or D-glucose. By contrast peritubular probenecid inhibited urate secretion from bath to lumen in all three segments (ID_{50} 0.9-2.6 10^{-4}M). The passive component of urate influx (probenecid resistant influx) was subtracted from the total influx of urate to estimate the facilitated component of urate secretion. Facilitated urate secretion was strongly dependent on the urate bath concentration, showing a sigmoidal (allosteric) relationship between urate secretion and bath concentration in S_1 and S_2 segments. The $S_{0.5}$ values of 197, 242 and 175x10^{-6}M obtained from Hill plots of data from S_1, S_2 and S_3 segments, respectively, indicates that the secretory mechanism has a relatively uniform affinity for urate along the proximal tubule. The V_{max} values for urate secretion were 591, 593 and 55x10^{-15}M/min/mm for the same segments. The kinetic analysis indicates that the axial heterogeneity of urate secretion is likely due to differences in the relative densities of common affinity urate transporters along the proximal tubule. We suggest that in the rabbit, at low plasma levels, urine urate is the product of glomerular filtration, passive reabsorption and minimal proximal secretion. With elevated plasma urate levels, the S_1 and S_2 segments avidly secrete urate, a feature of urate excretion that may be shared by most mammals.

EFFECT OF CARBONIC ANHYDRASE INHIBITION (CAI) ON THE PROXIMAL RESPONSE TO VOLUME EXPANSION. Martin G. Cogan and Floyd C. Rector, Jr. CVRI, Dept. of Med., U. of Calif., San Francisco, CA.

Absolute proximal reabsorption of water, bicarbonate and chloride (Cl) normally increase when SNGFR rises due to colloid-containing volume expansion; in contrast, colloid-free expansion causes a comparable increase in SNGFR but only bicarbonate, not water or chloride, reabsorption increases. To ascertain whether this difference depends on carbonic anhydrase activity, 22 Munich-Wistar rats were micropunctured during complete CAI (50 mg/kg acetazolamide) while volume contracted (hydropenia) and then while isohydrically expanded (Exp.) either with colloid-containing (plasma, 5% body weight) or with colloid-free (Ringer's bicarbonate, 10% body weight) solutions. End-proximal concentrations of total CO_2 as measured by microcalorimetry (32 ± 1 mM) and Cl (115 ± 3 meq/l) were both found to be only 3 meq/l higher than in Bowman's space in all groups.

	SNGFR	Absolute Proximal Reabsorption		
		H_2O	Total CO_2	Cl
	(nl/min)	(nl/min)	(pmol/min)	(peq/min)
CAI-Hydropenia	28±1	7.4±0.4	158±8	739±65
CAI-Plasma Exp.	45±1	12.0±0.5	291±16	1159±90
CAI-Ringer Exp.	46±1	7.9±0.5	147±20	790±89

During CAI with plasma expansion, the increments in absolute water and Cl reabsorption were similar in magnitude to those observed in the normal, uninhibited state. Conclusions: 1) The increase in absolute proximal reabsorption of water, Cl and bicarbonate when SNGFR rises with plasma expansion can occur in the absence of anion concentration gradients or carbonic anhydrase activity. 2) In contrast to normal, when Ringer expansion lowers peritubular protein concentration during CAI, the reabsorption of bicarbonate, as well as Cl and water, is reduced so that the reabsorptive process remains isohydric.

ROLE OF DEEP NEPHRONS (DN) AND DISTAL STRUCTURES (DS) IN THE BICARBONATURIC EFFECT OF ACETAZOLAMIDE (Az). M. Cruz-Soto,* K. Itsarayoungyen,* D.C. Batlle, J.A.L. Arruda, N.A. Kurtzman, (intr. by Robert Hedger). Univ. of ILL. Hospital, Chicago, ILL.

Micropuncture studies indicate that carbonic anhydrase inhibition (CAI) results in approximately 90% inhibition of proximal HCO_3 reabsorption (R) in superficial nephrons (SN); only 30% of the HCO_3 is excreted leaving 60% unaccounted. HCO_3 could be reabsorbed in DN and/or beyond the proximal tubule of SN. To investigate this issue we used the model of chronic papillary necrosis induced by 2 bromoethylamine (BEA) infusion which consistently results in more than 80% destruction of DN. No differences in fractional (F) HCO_3 excretion (Ex) were observed between BEA and control (C) rats after acute CAI induced by Az (32±1.2% vs 30±1.6%, NS). Superimposed blockade of distal HCO_3 R induced by amiloride (A) resulted in a similar increase in F HCO_3 Ex in BEA and C rats (to 41.7± 1.7% and 38±1.4% respectively, NS). To examine the contribution of the thick ascending loop of Henle (LH) in HCO_3 R, furosemide (FU) was infused to BEA and C rats receiving A+Az as above. This maneuver resulted in higher levels of F HCO_3 Ex in BEA than in C rats (52±1% vs 43±2.9%, $p<0.02$) indicating that the LH of SN contributes less than 10% to overall HCO_3 R. Our data suggest that DN and DS of all nephrons can account for approximately 20% of overall HCO_3 R during CAI. Thus, these structures cannot account for the 60% of overall kidney HCO_3 R that persists after CAI. If A and FU maximally inhibit HCO_3 R in DS, then our data indicate that superficial micropuncture does not accurately portray the relation of CAI to HCO_3 R.

MODIFICATION OF THE RENAL RESPONSE TO ACUTE UNILATERAL NEPHRECTOMY (AUN) BY METABOLIC ACIDOSIS (MA). S.B.Court,* H. Al-Bander,* and M.H.Humphreys. University of California Renal Center, San Francisco General Hospital, San Francisco, CA.

In 6 anesthetized, mechanically ventilated dogs (arterial pH 7.38, P_{CO2} 33 mmHg)(Group I), AUN increased sodium excretion ($U_{Na}V$) from 21.6±9.0 to 38.9±12.4 µEq/min ($p<.05$) and potassium excretion (U_KV) from 27.2±5.4 to 57.6±12.3 µEq/min ($p<.05$). Chloride excretion ($U_{Cl}V$) was unchanged, whereas bicarbonate excretion ($U_{HCO_3}V$) rose from 12.7±5.8 to 27.3±9.3 µmol/min ($p<.02$). In 6 other dogs (Group II), infusion of dilute HCl produced acute MA (pH 7.21, plasma HCO_3 concentration 15 mmol/L). AUN increased $U_{Na}V$ (8.8±3.5 to 30.3±9.6 µEq/min, $p<.05$) and U_KV (28.9±7.1 to 62.8±8.3 µEq/min, $p<.01$) by amounts similar to those seen in euhydric Group I dogs. $U_{Cl}V$ also increased significantly from 17.1±8.9 to 34.6±10.2 µEq/min ($p<.001$) in contrast to results in Group I, and a slight increase in $U_{HCO_3}V$ (Δ = 3 µmol/min) was less than the increase in Group I ($p<.02$). In neither group did plasma HCO_3 concentration, GFR, or ammonia or titratable acid excretion change as a result of AUN.

These results demonstrate that the increased cation excretion occurring after AUN in euhydric dogs is preserved in Group II dogs with acute MA. However, the pattern of anion excretion seen in Group I is altered by MA to reflect the altered filtered loads of Cl and HCO_3. The similar increase in U_KV after AUN in both groups despite a likely decrease in distal HCO_3 delivery in Group II dogs suggests that increased distal K secretion is not solely the result of increased luminal HCO_3 in the distal nephron. Other factors must contribute to increased U_KV after AUN.

EPINEPHRINE DECREASES DISTAL TUBULAR POTASSIUM (K) SECRETION. R.A. DeFronzo, G. Klein-Robbenhaar*, B. Stanton* and G. Giebisch. Yale University School of Medicine, New Haven, Ct.

Studies have shown that epinephrine (E) inhibits K excretion in man (Kid.Int. 16:917, 1979). We now examine the effect of E on proximal (PT) and distal (DT) tubular K transport in rats following an acute K load using micropuncture techniques. Three groups were studied: I-Controls (Ringer); II-KCL (5.1 µEq/min/100 gm); III-E (0.033 µgm/min/100 gm) + KCl. In controls P_K was 4.43±0.07, U_KV 0.41±0.05 µEq/min/100 gm and FE_K 18±3%. With KCL infusion P_K rose to 6.05±0.12 ($p<0.01$) and U_KV and FE_K to 1.57 ±0.09 and 50±2% ($p<0.001$). E inhibited ($p<0.01$) the rise in P_K (5.21±0.13), U_KV (0.93±0.05), and FE_K (31±2) without affecting GFR. Fractional delivery (TF/P)K/IN of K to the late PT (0.46±0.03) and early DT (0.09±0.02) was similar in all three groups. Late DT (TF/P)K/IN was 3.3 fold greater in KCl (0.52±0.06) vs. control (0.12±0.02; $p<0.001$) and was markedly reduced with E (0.24±0.04; $p< 0.001$). (U/P)K/IN in final urine was not increased above that in late DT in any group. E failed to affect the K-mediated increase in $U_{Na}V$ but significantly decreased urine flow.

CONCLUSIONS: (1) K infusion stimulates K secretion by the DT, (2) E effectively blocks the rise in U_KV following K loading by inhibiting DT K secretion, (3) this inhibitory effect of E may in part be mediated by changes in DT flow, (4) despite inhibition of U_KV, the rise in P_K was significantly less than KCl alone, indicating that E also enhances extrarenal K tolerance.

● ION TRANSPORT AS THE PACEMAKER OF CELLULAR METABOLISM IN THE TURTLE URINARY BLADDER. T.E.Dixon and Q. Al-Awqati. Depts of Medicine, SUNY, Stony Brook and Columbia University, New York, N.Y.

In the turtle bladder, the rate of H^+ transport (J_H) and sodium transport (J_{Na}) are tightly coupled to the rate of cellular oxidative metabolism (J_m). We showed previously that maneuvers which alter J_H are associated with changes in the cellular free energy of ATP hydrolysis (ΔG_{ATP}). The following experiments were done to test the interrelationships among ion transport, mitochondrial oxidative processes and cellular ΔG_{ATP}.

We measured J_H, rate of ^{14}C-glucose oxidation (J_{CO_2}*) and epithelial cell content of ATP, ADP and Pi simultaneously in well paired, ouabain treated hemibladders. Inhibition of J_H by mucosal acidification (n=5) caused a 48.2% decrease in J_{CO_2}*. This was associated with a significant increase in ATP/ADP·Pi ratio from 1972 to 3976 M^{-1} and a calculated increase in ΔG_{ATP} (assuming intracellular pH 7, [Mg] 1mM, temp 30°C) from 48.32±.38 to 50.23±.30 KJ/M.

In 3 experiments we measured J_{Na}, J_{CO_2}* and the cellular content of ATP, ADP and Pi simultaneously in acetalzolamide treated, well paired hemibladders. Inhibition of J_{Na} by mucosal amiloride caused a 56.9% decrease in J_{CO_2}*, an increase in the ATP/ADP·Pi ratio from 1063 to 2883 M^{-1} and an increase in ΔG_{ATP} from 46.98±.57 to 49.67±.19 KJ/M.

In preliminary studies the initial rate of oxygen consumption of mitochondria, isolated from the turtle liver, decreased linearly in response to exposure to increasing ambient ΔG_{ATP} from 43 to 56 KJ/M.

These studies demonstrate that the cytosolic ΔG_{ATP} is the signal that couples epithelial ion transport to oxidative metabolism.

● **EVIDENCE THAT AN ACID DISEQUILIBRIUM pH (pH Dq) IS A DETERMINANT OF PAPILLARY COLLECTING DUCT (PCD) PCO_2.** Thomas D. DuBose, Jr., and Leo R. Pucacco. Univ. of Texas Hlth. Sci. Cntr., Dallas, Tx.

The etiology of urinary CO_2 tensions exceeding that of systemic blood during bicarbonate loading (BL) remains controversial. This study was designed to measure and correlate PCO_2 and pH Dq at the base and tip of the PCD in the exposed papilla of the Munich-Wistar rat by micropuncture and microelectrode techniques. pH Dq was calculated as the difference between the directly measured in situ pH (pH Is) and equilibrium pH (pH Eq). Alkalosis without volume expansion was achieved by infusing 300 mM $NaHCO_3$ in 24 rats (BL). 14 of these rats subsequently received carbonic anhydrase i.v. (CA). The urinary pH and PCO_2 from the right kidney was 7.53 ± 0.12 and 139.4 ± 10.9 mm Hg. The mean PCO_2 in the PCD was 95.4 ± 4.1 (38) at the base and 122.2 ± 4.3 (52) at the tip during BL and fell to 68.1 ± 2.4 (44) (base) and 78.3 ± 2.8 (50) (tip) after CA ($p < 0.001$). pH Is was 7.29 ± 0.03 at the base and 7.35 ± 0.05 at the tip while pH Eq was 7.74 ± 0.06 (base) and 7.73 ± 0.08 (tip). Concomitant values for pH Dq were -0.42 ± 0.04 (48) (base) and -0.36 ± 0.03 (26) (tip) during BL ($p < 0.001$ vs. 0). The pH Dq was obliterated by CA at both sites. These findings represent the first direct measurement of both an elevated PCO_2 and a significantly acid pH Dq in the PCD during BL and support the hypothesis that H^+ secretion is an important determinant of the U-B PCO_2 gradient during excretion of an alkaline urine. The observed rise in urinary PCO_2 occurs along the PCD, not after exit from the papilla.

SHORT TERM EFFECT OF ALDOSTERONE ON Na-K-ATPase IN SINGLE TUBULES. Alain Doucet* and Adrian I. Katz, Dept. of Med., Univ. of Chicago, Chicago, IL.

One of the theories advanced to explain the effect of mineralocorticoids (MC) on ion transport postulates that MC binding to receptors triggers a sequence of events that leads to stimulation of the "sodium pump". To test this hypothesis we evaluated in vitro and in vivo the short term effect of d-aldosterone (A) on Na-K-ATPase in discrete nephron segments microdissected from adrenalectomized (ADX) and control (C) mice and ADX rabbits. Mice were studied 5-7 days after surgery, when Na-K-ATPase activity reached its nadir. Plasma A (pg. ml^{-1} ± SE) averaged 23 ± 4 in ADX mice compared to 605 ± 58 in C. In the in vitro experiments tubule segments were incubated before assay for 90 min at 37°C with or without A (3.10^{-10} - 3.10^{-6} M). In the in vivo studies mice received A, 10 µg per 100 g B.W. i.p., one or 3 hours before sacrifice. Results (pmoles $.mm^{-1}$ $.hour^{-1}$ ± SE) in the distal convoluted (DCT) and cortical collecting tubule (CCT) of the mouse were:

	DCT	CCT
ADX	1375 ± 149(16)	586 ± 64(17)
ADX + A in vitro	1248 ± 110(16)	579 ± 67(17)
ADX	1488 ± 132(13)	478 ± 58(15)
ADX + A in vivo (1h)	1215 ± 107(15)	513 ± 37(15)
ADX + A in vivo (3h)	1517 ± 265(9)	447 ± 76(9)
C	4978 ± 295(6)	1141 ± 75(6)
C + A in vivo (1h)	4442 ± 282(6)	993 ± 73(6)

Results in vitro with rabbit tubules were similar.

These studies did not show a short term effect of aldosterone either in vivo or in vitro on renal tubular Na-K-ATPase and therefore do not support the "pump theory" of mineralocorticoid action.

PLASMA OSMOLALITY (P_{OSM}) IN PREGNANT RATS IN THE ABSENCE OF VASOPRESSIN (AVP) AND DURING ANGIOTENSIN BLOCKADE. J.A.Durr*, B.A.Stamoutsos* and M.D. Lindheimer, Dept.of Obstet.& Gynecol.and Med. Univ. of Chicago, Chicago, Ill.

Plasma tonicity and the threshold for AVP secretion are ≃11 mOsm/kg lower in pregnant Sprague Dawley rats than in age-matched controls (Kidney Int.16:871). Studies were designed to further investigate why P_{osm} decreases during gestation. Basal P_{osm} was 281±SD4 mOsm/kg in 20 day gravid and 292±4 mOsm/kg in controls ($p < .001$) while P_{AVP} was 2.2±0.8 and 2.1±2.2 pg/ml in pregnant and control rats respectively (NS). Water loading (30 ml/kg) resulted in prompt urinary dilution and rapid excretion of the load in both pregnant and virgin animals demonstrating that the reset osmostat during pregnancy is not associated with non suppressible AVP secretion in the basal state. Captopril (100 mg/kg i.p.) twice daily for 5 days didn't affect P_{osm} in either gravid (282±4 mOsm/kg) or control (292±4 mOsm/kg) rats and P_{osm} was similar to controls after 14 days of estrogen and/or progesterone treatment using doses which produce levels at least as high as those in pregnancy.

In separate studies P_{osm} was measured in Brattleboro rats which produce no AVP. Values in pregnant homozygous (DI), heterozygous, and Long Evans animals were 292±4, 286±5, and 284±3 mOsm/kg compared to 310±6, 300±3, and 292±2 mOsm/kg in virgins; while U_{osm} in the basal state was similar in gravid and control animals of each group. Conclusion: The decrement in P_{osm} during pregnancy occurs in the absence of AVP. Neither estrogen, progesterone nor the renin-angiotensin system appear responsible for these changes.

● VASOPRESSIN (VP) SENSITIVE cAMP SYSTEM IN THE ISOLATED PAPILLARY COLLECTING DUCT (PCD): MODULATION BY PGE_2. R.M. Edwards,* B.A. Jackson,* and T.P. Dousa: (intr. by D.N. Wochos). Mayo Clinic, Rochester, MN.

By modifying the tissue preparation procedure we have been able to dissect intact PCD from rat kidney and have studied the effects of VP and PGE_2 on the cAMP system. All enzyme assays and incubation were performed in media whose osmolality was increased to 800 mosM by addition of NaCl and urea. Adenylate cyclase activity (AdC) in disrupted PCD was stimulated in a dose-dependent way by VP ($\frac{1}{2}$ max. dose 10^{-9}M VP; max. dose 10^{-6}M VP, Δ%+655%). Addition of 10^{-6}M PGE_2 had no effect on AdC activity in the PCD, but 10^{-5}M PGE_2 caused an increase in AdC activity (Δ+335%). PGE_2 had no additive or inhibitory effect on VP-stimulated AdC activity. Incubation of intact PCD with 10^{-5}M PGE_2 caused a small (6.1±1.9 to 11.4±2.8 fmol/mm) increase in basal cAMP levels, but 10^{-6}M or 10^{-4}M PGE_2 had no significant effect on cAMP levels. In contrast, VP-stimulated cAMP accumulation in intact PCD was markedly inhibited by about 50% by 10^{-5}M PGE_2:

	mean ± SE (fmol cAMP/mm)	
Basal:	4.5 ± 0.7	P<0.005
VP 10^{-8}M:	32.5 ± 3.7	P<0.01
VP+PGE_2:	19.1 ± 3.2	

Preincubation of PCD with 10^{-5}M PGE_2 did not change the activity of cAMP-PDIE. Present results demonstrate an active VP-sensitive cAMP system in the PCD. While PGE_2 does not inhibit VP-stimulated AdC activity or activate cAMP-PDIE in PCD, it inhibits the stimulatory effect of VP on cAMP accumulation in intact PCD. Results suggest that in PCD, hydroosmotic action of VP is antagonized by PGE_2 at the step of cAMP accumulation.

DO EXTREME CHANGES IN ATMOSPHERIC PRESSURES AFFECT THE NORMAL OSMOREGULATION? P.U. Feig, P. Mitchell* D.M. Stetson* and L.W. Raymond*: (intr. by M. Galen). Univ. Conn. School of Med., Farmington, CT and U.S. Navy, CSDG-1, San Diego, CA.

Previous findings (Lambertsen, et al, 1978) suggesting that exposure to extreme atmospheric pressures caused an increment in plasma [Na] (P_{Na}) and osmolality (P_{osm}) in normal subjects despite free access to water, prompted the present studies.

Six volunteers were exposed to the equivalent of 1,520 feet of water (FSW) in a pressure chamber. P_{Na}, Posm and maximal urinary osmolality (U_{max}) after overnight water deprivation were measured immediately before (O FSW), during (1,000 and 1,520 FSW), at the end (18 FSW) and one week after (O FSW) exposure. Results (mean ± SD) in mEq/L and mOsm/Kg H_2O were:

Day	FSW	P_{Na}	Posm	U_{max}
1	0	140.2 ± 3.9	287.8 ± 4.7	961.3 ± 141.0
10 & 12	1,000 & 1,520	140.6 ± 1.9	290.5 ± 3.4	796.2 ±* 149.2
37 & 44	18 & 0	137.8 ± 2.6	285.5 ± 7.2	925.3 ± 78.0

A water load (20 ml/kg) performed on day 36 (35 FSW) on 5 volunteers yielded incomplete excretion by 5 hours in 3, and a maximally dilute urine (U_{min}) of 195 mOsm/Kg H_2O in one.

The previously found increment in P_{Na} and Posm after exposure to similar hyperbanic levels was, therefore, not confirmed. The significantly lowered U_{max} (*$p < 0.05$) and abnormal U_{min} (either insufficient or too transient in 3 out of 5 individuals) may represent an osmoregulatory abnormality which needs further evaluation.

OSMOLAR INFLUENCES ON URINARY ACIDIFICATION AND METABOLISM IN THE COLOMBIAN TOAD BLADDER. Herve Favre*, Kay Hwang*, and Jacques J. Bourgoignie. Univ. of Geneva, Switzerland and Miami, Florida.

Changes in extracellular fluid tonicity influence sodium transport across the isolated toad bladder. We determined the ion specificity of these osmolar effects by examining the acidification current in the Colombian toad bladder exposed to 0.125 mM amiloride in iso-(236 mOsm/kg H20), hypo-(147 mOsm) and hypertonic (306 mOsm) media. The Ringer's tonicity was modified by changing the sodium concentration while keeping the other constituents constant. Amiloride reversed short circuit current (RSCC) to -24 ± 2 μAmp/2 cm^2 in isotonic Ringer. Hypertonicity reduced RSCC to -3 ± 2 μAMP while hypotonicity increased it by 50%. These effects stem from a serosal, mucosal-independent, sensitivity to tonicity changes. They are independent of sodium transport since they occur in choline-Ringer or in the absence of serosal K^+ and mucosal Cl^-. Moreover, acetazolamide completely inhibits the negative SCC elicited by amiloride and stimulated by hypotonicity. In separate experiments amiloride inhibited ^{14}C-pyruvate oxidation by 54 ± 6%, from a control value of 6106 ± 552 nmoles/gm dry wt per hr. Hypotonicity stimulated and hypertonicity further reduced the amiloride inhibited cell metabolism. Acetazolamide prevented the stimulation of pyruvate oxidation by hypotonicity.

In summary, like sodium transport, the acidification current is inhibited by serosal hypertonicity and stimulated by serosal hypotonicity. These changes in transport are associated with concurrent changes in cell metabolism.

ADRENERGIC AND DOPAMINERGIC RECEPTORS IN GLOMERULI (G) AND CORTICAL TUBULES (CT). R.Felder*, L.Schoelkopf*, J.Pelayo*, M.Blecher*, P.Calcagno, G.Eisner, and P.Jose. Depts. of Biochem, Peds, Med, and Physiol and Biophys. Georgetown Univ. Med. Ctr., Washington, D.C.

We have previously characterized alpha (AAR) and beta (BAR) adrenergic receptors in partially purified renal tubular plasma membranes both in dogs and in rats. In the present studies we compared AAR, BAR and dopaminergic receptors (DR) in cortical tubules (CT) and in glomeruli (G) of rats on an unrestricted salt intake. G and CT were separated by sieving. Dissociation constant (K_d) in nM and receptor occupancy (R_o) in pmol/mg protein were determined using ^3H-WB4101 and (-)-norepinephrine for AAR, ^3H-dihydroalprenolol and (-)-propranolol for BAR and ^3H-haloperidol and cis-flupenthixol for DR. The mean results ± SEM are tabulated:

Tissue		AAR (n=6)	BAR (n=9)	DR (n=6)
G	K_d	1.86±0.60	186±23.65	6.98±1.51
	R_o	0.23±0.09	2.99±0.42	0.24±0.10
CT	K_d	1.18±0.18	179±19.25*	30.70±7.29*
	R_o	0.23±0.07	1.26±0.12	1.20±0.49*

* $p<0.05$ G vs CT

G and CT showed similar values for AAR both for K_d and R_o. The K_d for BAR was similar in G and CT but R_o for BAR was higher in G than in CT. In contrast, the studies of DR showed both a higher K_d and R_o in CT than in G. Catecholamines have been shown to affect cyclic nucleotide production in G and CT. The differing patterns of receptor concentration demonstrated may be a clue to the differing effects of these agents on nephron function.

HOMOCYSTINE UPTAKE BY RAT RENAL CORTICAL TUBULES
J. Foreman*, H. Wald*, G. Blumberg*, L. Pepe*, S. Segal
The Children's Hospital of Philadelphia, Dept. of Pediatrics, Univ. of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

A shared transport system for homocystine and the dibasic amino acids has been postulated to explain increased homocystine excretion after lysine infusion in homocystinuric patients. To study in more detail the nature of the renal handling of homocystine, we examined the cellular uptake of ^{35}S-homocystine by isolated renal cortical tubules. Homocystine at 0.025mM concentration was progressively taken up by the tubules reaching a steady state radioactive distribution ratio of 10 by one hr of incubation. Analysis of the intracellular pool revealed that the majority of the transported homocystine had been converted to cystathionine, but concentrative uptake of homocystine was demonstrable after 30 min of incubation. Homocystine uptake was oxygen dependent. A kinetic analysis of the concentration dependence revealed that two systems for homocystine uptake were present (K_{m1}= 7.65mM, K_{m2}=0.171mM). Cystine, lysine, arginine and ornithine all inhibited the initial uptake of homocystine, while proline and glycine had no effect. The presence of 3mM lysine or arginine altered the kinetic parameters of homocystine uptake such that only one component of transport was observed corresponding to the high K_m system. Our data indidate that homocystine is actively transported by two saturable systems of which the low K_m system is inhibitable by the dibasic amino acids. This pattern of uptake for homocystine resembled that observed by us for cystine. Exploitation of this transport interaction may be useful in lowering plasma levels in patients with homocystinuria.

HEAD-OUT WATER IMMERSION (WI) DOES NOT INDUCE NATRIURESIS IN THE AWAKE DOG. P. Frommer*, W. N. Suki and J. C. Ayus. Renal Section, Baylor College of Medicine, Houston, Texas.

Head-out WI induces significant systemic hemodynamic changes and a natriuresis in man. However, this maneuver has not been studied in the awake animal. The present study was undertaken to evaluate the effects of head-out WI in 53 awake dogs.

Four groups of animals were studied: Group 1 (from 8 AM to 4 PM; time control); Group 2 (from 8 AM to 4 PM; WI at bath t° 36°C); Group 3 (from 2 PM to 10 PM; WI at bath t° 36°C) and group 4 (from 2 PM to 10 PM; WI at bath t° 33°C). Significant increases were observed in all 3 immersion groups in V (0.34 ± 0.10 to 0.98 ± 0.26 ml/min; P<0.01; mean ± SE); GFR (55.7 ± 6.6 to 93.2 ± 9.8 ml/min; (P<0.01); C_{PAH} (179.9 ± 19.3 to 244.4 ± 19.5 ml/min P<0.05); mean arterial blood pressure (136.3 ± 3.0 to 146.4 ± 2.0 mmHg; P<0.01); mean pulmonary artery pressure (17.6 ± 1.0 to 26.0 ± 1.0 mmHg; P<0.01) and cardiac output (2.80 ± 0.16 to 4.07 ± 0.23 l/min; P<0.001). $U_{Na}V$ only increased with WI in group 2 from 46.4 ± 11.3 to 102.8 ± 23.8μEq/min (P<0.01), however, this increase was not significantly different from the increase observed in group 1 (time control). Thus, our results show (1) head-out WI induces reproducible systemic and renal hemodynamic changes regardless the time of day or temperature of the bath (2) the changes in $U_{Na}V$ associated with WI are the result of spontaneous diurnal variation. These findings show that head-out WI in the awake dog does not induce a natriuresis in spite of significant systemic and renal hemodynamic changes.

EFFECT OF FASTING ON RENAL ADAPTATION TO DIETARY AMINO ACID CHANGE. Aaron L. Friedman, Russell W. Chesney*, and Patti W. Albright. University of Wisconsin Med. School, Dept. of Pediatrics, Madison, Wisconsin.

We have previously shown changes in the renal handling of the amino acid taurine (T) with alteration of T in the diet. This adaptation develops within 3 days of starting the diet and is complete within 10 days. Adult rats were fed 1 of 3 diets for a 2 week period: high T (HTD), 3%T; normal experimental (NX); low T (LTD), no T, low cysteine, methionine. Half the rats were then fasted (water only) for 3 days. Weight loss averaged 15% (range 13-22%). Renal transport of T was assessed in fasted and fed rats using isolated renal cortical tubule segments. Uptake of 0.01mMT was measured, after 5 minutes incubation, by isotopic distribution ratio as depicted below (± SEM)

	HTD	P	NX	P	LTD
Fed	6.08±.37	<.01	10.54±.21	<.01	20.14±.68
P	NS		NS		<.05
Fast	8.50±1.09	<.1	14.23±1.09	NS	15.60±.57

Fed animals demonstrated renal tubule adaptation to dietary change with enhanced uptake of T in LTD and diminished uptake in HTD. Fasted animals showed marked blunting of the adaptive response with no significant difference seen among the diet groups. Little difference is seen between fasted and fed rats on HTD or NX. With LTD protein catabolism secondary to fasting provides cysteine and methionine which can be metabolized to T. The increased T load may then serve to reverse the renal adaptation.

RENAL CELL ULTRASTRUCTURE DURING ONTOGENY AND COMPENSATORY HYPERTROPHY. A STUDY USING NEW THICK-SECTION TECHNIQUES. P. Gaffiero*, G. Thiéry* and M. Bergeron, Dép. de physiologie, Université de Montréal, Montréal, Québec. (Intr. S. Carrière).

The histological observation of thick sections (0,5-1,5 μm), with a standard transmission EM (80-100 Kv), combined with stereomicroscopy, permits a three-dimensional view of cell organelles which were studied during ontogeny and after a uninephrectomy.

The ontogeny of the endoplasmic reticulum (ER) of the rat nephron was studied following a five-day impregnation in OsO_4 (1). In the foetus, the nuclear sac is first stained; then the tubular structures of the ER and the Golgi apparatus seem to develop. As maturation advances, the tubular structures form a network and the fenestrated saccules, seen in adult cells, appear. Seven days after birth, most cells have an ER network extending from the apex to the base.

After uninephrectomy, tubular structures of the ER appear to proliferate at the base and the apex forming a very dense network; fenestrated saccules are much less numerous and many are seen at the apex. Many cells are not impregnated with osmium due probably to a functional difference.

The lead and copper block-staining technique previously described (2) was used to study mitochondria which, in immature renal cells, are rather small and not numerous; many are localized near the cell membrane and the ratio of nucleus/cytoplasm is high. They frequently seem to be arranged in clusters although the winding network of the chondriome is apparent only in mature cells.

(1) Thiéry, G., 1979, Biol. Cell 35, 159-164. (2) Bergeron, M. et al., 1980, Kidney Int. 17, 175-185.

EFFECT OF CONVERTING ENZYME INHIBITORS (CEI) ON PROSTAGLANDIN SYNTHESIS BY ISOLATED RAT GLOMERULI. M. Galler*, V.W. Folkert and D. Schlondorff. Albert Einstein College of Medicine, Bronx, N.Y.

Locally produced prostaglandins (PG) influence glomerular function. Recently, improvement of GFR has been reported to occur with CEI in congestive heart failure (Dzau et al. N. Eng. J. Med. 1980) and circulating PGE_2 levels were increased in patients treated with captopril (SQ 14225) (Swartz et al. J. Clin. Invest. 1980). We therefore investigated the effect of CEI on PG synthesis by isolated rat glomeruli. Glomeruli were incubated ± the experimental agents and PGE_2 and $PGF_{2\alpha}$ were determined by RIA. SQ 20881 (25μM) slightly increased PGE_2 synthesis from control values of 2688±917 pg/mg prot x 10 min to 2911±984 (n=4; P<0.1) but decreased $PGF_{2\alpha}$ from 4201±1395 to 3336±1465 (n=5; P<0.02). Captopril SQ 14225 (25μM) caused a greater stimulation of PGE_2 synthesis from 2149±673 to 3079±977 (n=6; P<0.05) and a stronger inhibition of $PGF_{2\alpha}$ from 4201±1395 to 2390±966 (n=5; P<0.02). Stimulation of PGE_2 and inhibition of $PGF_{2\alpha}$ by either CEI was dose dependent. Aprotinin (1.6μM) a kallikrein inhibitor, did not alter the effect of either CEI on PG synthesis. We conclude therefore that the action of CEI on prostaglandin synthesis by the glomerulus seems to be direct and independent of locally generated kinins. The combination of increased PGE_2 and decreased $PGF_{2\alpha}$ synthesis by CEI may be related to their effect on glomerular function.

● MINERALOCORTICOID STIMULATION Of NA-K-ATPASE IN NEPHRON SEGMENTS. L. Garg,* M. Knepper, and M. Burg, LKEM, NHLBI, Bethesda, MD.

We measured Na-K-ATPase in various nephron segments of control rabbits and following 5 mg deoxycorticosterone (DOCA)/day for 8-11 days or low salt diet (which increases endogenous aldosterone) for 12-18 days. Tubules were dissected, and their ATPase was determined by coupling ATP hydrolysis to oxidation of NADH, (measured by fluorometry). Na-K-ATPase was defined by ouabain inhibition. In control rabbits the Na-K-ATPase, pmol/mm tubule/min ± SEM (number of rabbits), was:

Proximal convoluted tubule, S1	105±17(6)
" straight " , S2	40± 2(4)
" " " , S3	23± 3(4)
Thin descending limb	4± 2(4)
" ascending "	3± 4(4)
Medullary thick ascending limb	124±23(4)
Cortical " " "	31± 3(5)
Distal convoluted tubule	152±20(6)
Connecting tubule	126±15(7)
Cortical collecting duct	23± 2(4)
Outer medullary " "	19± 4(7)

The enzyme activity was directly proportional to the rate of sodium transport previously measured in these segments (r=.94). DOCA significantly affected Na-K-ATPase only in connecting tubules (to 254±32(7)) and cortical collecting ducts (to 143±14(4)). Low salt diet significantly affected it only in the latter (to 72±10(4)). The increases in the collecting ducts correlated with previously measured increases in sodium transport (r=.99). We conclude that chronic mineralocorticoid stimulation causes a large increase in Na-K-ATPase in cortical collecting ducts.

EFFECT OF ORTHOVANADATE (VO_4) ON URINARY CONCENTRATION AND DILUTION: IN VIVO AND IN VITRO STUDIES. Milton E. Garcia,* and Christof Westenfelder, Univ. of Illinois, Chicago, Illinois.

We showed previously that VO_4 inhibited proximal tubular reabsorption of PO_4, HCO_3, and glucose in rats by inhibition of Na-K-ATPase activity. Since it has been reported that VO_4 blunted the rise in water transport in response to vasopressin (VP) in the toad bladder, we examined whether 1)VO_4 inhibited free water clearance (CH_2O) in Brattelboro rats (N=8), 2)whether free water reabsorption (TCH_2O) in normal rats (N=13) was depressed by VO_4 and 3)whether VO_4 inhibited cAMP generation in slices of white medulla of rats and dogs, when stimulated by VP. Results: 1)VO_4 caused a 50% depression in CH_2O (p<0.001) at any level of distal Na delivery (CH_2O+CNa/GFR), while urine flow rose and GFR remained unaltered. 2)TCH_2O/ GFR was significantly reduced at all levels of osmolar clearance/GFR (p<0.001) during HCO_3 infusion. 3)cAMP generation in inner medullary slices from rats (N=6) and dogs (N=6) when stimulated with aqueous VP (2U) rose from 1.12±0.1 to 7.05±0.31 pmol/mg wet wt and from 1.71±0.32 to 8.12±0.42 pmol/mg wet wt (p<0.001) for both respectively. Addition of 10^{-3} M VO_4 to the incubate caused a 40 and 50% reduction in cAMP levels in tissues from rats and dogs (p<0.001 in both). These data demonstrate that VO_4 inhibits salt reabsorption in the thick ascending limb and H_2O reabsorption in the collecting duct. The inhibition of TCH_2O may result from impaired salt transport in the thick ascending limb and possibly from VO_4's inhibition of the VP induced rise in cAMP levels.

ALDOSTERONE(A)-INDUCED PROTEINS (AIPs) IN TOAD URINARY BLADDERS (TUBs): RELATIONSHIP TO Na+ TRANSPORT. M. Geheb*, G. Huber*, E. Hercker*, and M. Cox. VA Med. Cntr. and Univ. Pa. Sch. Med., Phila., Pa.

We have previously demonstrated AIPs in cytosolic, microsomal and mitochondrial fractions of TUB epithelial cells. The present studies were designed to examine the relationship between AIP synthesis and Na+ transport. Paired hemibladders (HBs) were mounted as bags and short-circuit current (SCC) was used to measure Na+ transport. In protocol I, one HB received A (10^{-7}M) and the paired HB received carrier (n=6). In protocol II, one HB received amiloride (AM; 10^{-3}M) and both HBs received A (n=3). In protocol III, one HB received antidiuretic hormone and theophylline (ADH+T; 100 mU/ml and 10 mM, respectively) and the paired HB received carrier (n=3). After 6 hr incubation, ^{35}S-methionine (60-120 μCi/ml) was added and the incubation was continued for an additional 4 hr. New protein synthesis was analyzed by 2-dimensional polyacrylamide gel electrophoresis and autoradiography. In protocol I, AIPs of similar size (70-80,000 daltons) and iso-electric points (5.7-6.2) were identified in all 3 subcellular fractions. In protocol II, AM had no effect on AIP synthesis even though it abolished A-stimulated SCC. In protocol III, ADH+T did not induce the synthesis of proteins similar to the AIPs even though SCC was markedly stimulated. Since AIP synthesis occurs in the absence of Na+ transport and since proteins with characteristics of the AIPs are not synthesized when Na+ transport is stimulated by ADH+T, AIP synthesis is not a non-specific consequence of the cellular metabolic changes associated with Na+ transport.

CONTROL OF DISTAL NEPHRON HYDROGEN ION SECRETION (DNHS) IN VIVO. M.B. Goldstein, S.C. Tam*, A. Gougoux*, B.J. Stinebaugh and M.L. Halperin. Univ. of Toronto, Toronto, Canada, Univ. of Montreal, Montreal, Canada and Baylor College of Medicine, Houston, Texas, USA.

The purpose of this study was to evaluate factors which influence DNHS in the intact animal. Specifically, the effect of distal sodium and/or bicarbonate (BIC) delivery on DNHS was investigated in dogs with a normal or greatly expanded ECF volume. The urine minus blood PCO_2 difference in alkaline urine (U-B PCO_2) was measured to reflect DNHS in vivo. Bicarbonaturia was induced in normal dogs by the infusion of small or large quantities of sodium BIC. When this infusion rate was low (0.4 ml/min, 150 mM), the dogs remained in sodium balance (+ 4.8 ± 1.4 mEq). The U-B PCO_2 did not correlate with the urine BIC concentration (U BIC = 220 ± 16 mM; U-B PCO_2 = 0.18 U BIC + 55, r = 0.35). However, a significant correlation was obtained with sodium excretion ($U_{Na}\dot{V}$); (U-B PCO_2 = 1.1 $U_{Na}\dot{V}$ + 1, r = 0.75). In contrast, in dogs receiving a large sodium BIC load (1-2 ml/min, 900 mM), total body sodium increased about 1.2-fold. There was no correlation between the U-B PCO_2 and the $U_{Na}\dot{V}$, but there was now a significant correlation between the U-B PCO_2 and the U BIC (U-B PCO_2 = 0.17 U BIC + 5, n = 200, r = 0.87). At comparable U BIC (~ 200 mM), the U-B PCO_2 in normovolemic dogs was much higher than in ECF volume expanded dogs (91 vs 45 mm Hg). Conclusion: The U-B PCO_2 can either be a function of $U_{Na}\dot{V}$ or U BIC dependent on the ECF volume of the animals.

● ELEVATED URINARY pCO_2-AN INTRARENAL EVENT. ML Graber*, CR Caflisch*, HH Bengele, EA Alexander. Thorndike Mem. Lab., Renal Section, Boston City Hosp., Depts Med. & Phys., Boston Univ. Med. Sch., Boston, Mass.

To evaluate the hypothesis that elevated urinary pCO_2 reflects post-papillary delayed dehydration of H_2CO_3, we directly measured pCO_2 along the inner medullary collecting duct (IMCD) of the rat.

$NaHCO_3$ 0.3 M, was infused at 6.6 cc for 1 hr and continued at 3.3 cc/hr over 2 clearance periods while respiration was controlled. A pCO_2 microelectrode was inserted axially to obtain paired measurements of pCO_2 at 50% and 98% (tip) IMCD length. Measurements were made in 5 rats before (14 pairs) and during (13 pairs) carbonic anhydrase (CA) infusion (10 mg + 3.3 mg/hr) and in 5 time control (TC) rats which did not receive CA (13,11 pairs). Results are mean ± SEM.

	pCO_2 50%	pCO_2 98%	pCO_2 arterial	pH 98%
No CA-TC	64 ±5	71 ±4	38 ±1	7.80 ±.05
No CA-TC	80 ±5	84 ±4	39 ±1	7.71 ±.05
No CA	68 ±6	78 ±5	40 ±1	7.81 ±.09
CA	48 ±3	57 ±3	36 ±1	8.16 ±.10

We found that 1) IMCD pCO_2 increased between 50 and 98% in both periods of both groups (all $P < .05$) 2) IMCD pCO_2 considerably exceeded arterial pCO_2, and 3) CA reduced IMCD pCO_2 ($P < .01$) but not to arterial levels. We conclude that elevation of urinary pCO_2 is an intrarenal event and is not dependent on post-papillary phenomena. Part of this urine-blood gradient (10-20 mmHg) is independent of delayed dehydration since it was not abolished by CA.

HOW ACIDEMIA STIMULATES DISTAL NEPHRON HYDROGEN ION SECRETION (DNHS) IN THE DOG. A. Gougoux*, S.C. Tam*, P. Vinay, G. Lemieux, M.A. Duran*, M.B. Goldstein, B.J. Stinebaugh and M.L. Halperin. Univ. of Montreal, Montreal, Canada, Univ. of Toronto, Toronto, Canada and Baylor College of Medicine, Houston, Texas, USA.

The purpose of this study was to determine the mechanism whereby acidemia stimulates DNHS. We have shown that DNHS is stimulated by two processes; first, in dogs with a normal ECF volume, distal sodium delivery and avidity are the primary determinants of DNHS. Second, in dogs with an expanded ECF volume, DNHS is influenced by the urine bicarbonate concentration (U BIC). In normovolemic dogs, amiloride (AM) (a drug which inhibits sodium reabsorption in the DN) causes the U-B PCO_2 to fall from 62 ± 7 mm Hg to 5 ± 1 mm Hg at comparable U BIC (62 ± 4 and 52 ± 2 mEq/L); in the presence of AM, there is a correlation between U-B PCO_2 and U BIC (U-B PCO_2 = 0.18 U BIC - 14, r = 0.76). In contrast, in hypervolemic dogs, the U-B PCO_2 fell slightly with AM (10 mm Hg at a U BIC = 200 mM). The U-B PCO_2 remained strongly dependent on U BIC before (U-B PCO_2 = 0.19 U BIC + 5, r = 0.86) and after AM (U-B PCO_2 = 0.26 U BIC - 26, r = 0.75). There was a direct correlation between U-B PCO_2/U BIC and the blood (H^+) both before (U-B PCO_2/U_{HCO_3} = 0.046 (H^+) - 0.87, r = 0.86) and after AM (U-B PCO_2/U_{HCO_3} = 0.023 (H^+) - 0.36, r = 0.72). Conclusion: The U-B PCO_2 is directly related to Na reabsorption and is sensitive to AM when the ECF volume is normal. During ECF volume expansion, U BIC seems to influence DNHS and this process is stimulated by acidemia and no longer sensitive to AM.

● THE MECHANISM OF CHLORIDE TRANSPORT ACROSS THE BASOLATERAL MEMBRANE OF THE NECTURUS PROXIMAL TUBULE CELL. William Guggino*, Emile Boulpaep and Gerhard Giebisch (intr. F.Finkelstein). Yale Univ., Dept. Physiology, New Haven, CT 06510.

We have shown that the Cl^- conductance of the basolateral membrane of the Necturus proximal tubule cell is low. The purpose of this study is to characterize further the movement of Cl^- across the basolateral membrane using Cl^- sensitive liquid ion exchange and pH sensitive Thomas type glass microelectrodes. In control, intracellular Cl^- activity (a_{Cl}), 13.2±.7mM(51) is above the equilibrium value predicted from the basolateral membrane potential (V_{bl}) of -66±1mV(51). When Cl^- is lowered to 6 mM in only the basolateral solution a_{Cl} falls to 9.9±.7mM(15). When SITS ($5x10^{-4}$M) is applied for 15 min to both apical and basolateral bathing solutions, lowering only basolateral Cl^- does not affect a_{Cl} suggesting that SITS blocks the exit of Cl^-. When Cl^- is lowered in the basolateral solution in the absence of HCO_3^- (constant pH), a_{Cl} does not change significantly from control, 11.6±1.1mM(13) indicating that HCO_3^- is required for Cl^- exit. Changing pH in the basolateral solution from 7.6 to 6.8 by lowering HCO_3^- at constant pCO_2 causes intracellular pH to drop from 7.30±.04 to 7.09±0.06(6), a_{Cl} to rise from 12.7±1.3mM to 17.7±2.2mM(12), and V_{bl} to depolarize from 67±2mV to 46±3mV(12). Because the depolarization of V_{bl} during acidification does not reverse the outward electrical driving force for Cl^- across the basolateral membrane, these data suggest that the rise in a_{Cl} is linked to a drop in intracellular HCO_3^-. Conclusion: A pathway for Cl/HCO_3 exchange exists across the basolateral membrane of Necturus proximal tubule.

RELATIONSHIPS BETWEEN OXIDATIVE METABOLISM AND TUBULAR ABSORPTION OF FLUID, PHOSPHATE, AND GLUCOSE. S.R. Gullans*, P.C. Brazy, V.W. Dennis, and L.J. Mandel*. Departments of Physiology and Medicine, Duke University Medical Center, Durham, NC

Relationships between oxidative metabolism and proximal solute transport remain uncertain because of limitations inherent in studies using clearance or cortical slice techniques. In this study, net absorption rates for sodium (Jv), phosphate (J-Phos), and glucose (J-Gluc) were measured in isolated and perfused rabbit proximal convoluted tubules during changes in oxidative metabolism. Transport rates were determined with radioisotopes. In addition, metabolic events were monitored in suspensions of rabbit cortical tubules by measuring oxygen consumption rates (QO_2) and mitochondrial NADH fluorescence. Standard artificial fluids were used for control conditions. Metabolism was altered with rotenone, an inhibitor of NADH dehydrogenase; CCCP, an uncoupler of oxidative phosphorylation; or succinate, a mitochondrial substrate. Results are expressed as percent change from control ± SE.

	QO_2	Jv	J-Phos	J-Gluc
Rotenone (1 μM)	-79±3	-84±4	-85± 5	-59±6
CCCP (1 μM)	+51±2	-64±9	-70± 8	-42±6
Succinate (1 mM)	+66±7	+12±8	+65±13	+12±3

Rotenone and CCCP, known inhibitors of ATP synthesis, caused expected changes in QO_2 and inhibited Jv, J-Phos, and J-Gluc. Succinate stimulated QO_2 and increased J-Phos substantially but did not affect Jv or J-Gluc. Thus, these data indicate that variability appears to exist in the linkage of specific solute transport processes to changes in oxidative metabolism.

KINETICS OF POTASSIUM SECRETION IN MAMMALIAN COLON. Jonathan Halevy*, Henry J. Binder*, Patricia Pace* and John P. Hayslett, Beilinson Medical Center, Sakler School of Medicine, Tel-Aviv, Israel and Yale School of Medicine, New Haven, Connecticut

Although active potassium (K) secretion has been demonstrated in mammalian colon, the relative importance of pump versus passive mediated modes of transport has not been determined. Since saturability of the secretory mechanism would reflect a carrier mediated pathway, studies were performed in rat colon to define the kinetics of K secretion. Net K movement was determined during in vivo luminal perfusion prior to and following the infusion of KCL into the mesenteric artery. K concentration was assessed in samples of portal vein plasma and ranged from 3.8 mEq/L (prior to KCL infusion) to approximately 20 mEq/L during KCL infusion.

During infusion of KCL net K secretion increased 100% from control, (1.8 μEq/min/g dry tissue), and achieved a maximal level at a portal vein K concentration of 9 to 10 mEq/L. Net K movement conformed to Michaelis-Menten kinetics, and showed a Km of 5.0 mEq/L and Vmax of 3.6 μEq/min/g dry tissue. These results indicate that passive driving forces acting via paracellular pathways play a minor role in colonic secretion of K, and suggest that K secretion is primarily dependent on the pump mechanism in basolateral cell membrane.

EFFECTS OF EARLY AND LATE REDUCTION OF RENAL PERFUSION PRESSURE (RPP) ON THE NATRIURESIS (FeNa) OF VOLUME EXPANSION (VE) AND NEPHROGENOUS cAMP (NcAMP). V. Gura, R.M. Friedler, and S.G. Massry. Div. Neph., Dept. Med., USC Sch. Med., Los Angeles, CA.

Prior data showed that both VE and renal vasodilatation are associated with natriuresis and increased NcAMP. Studies were done to examine the effect of VE on sodium excretion and NcAMP during early or late reduction RPP in an effort to define the role of renal vasodilatation on NcAMP during VE. In 8 thyroparathyroidectomized (TPTX) dogs RPP to the left kidney was reduced (123±2.3 to 65±5.7 mmHg), VE was then produced and finally RPP was allowed to rise to 113±14.8 mmHg (group I). In 8 TPTX dogs VE was produced and then followed by a reduction in RPP (125±3.6 to 78±5.2 mmHg; group II). Cyclic AMP was measured in aorta, renal veins and urine. In group I, renal plasma flow (RPF), FeNa, urinary NcAMP (UNcAMP) and renal vein NcAMP (RVNcAMP) did not change in the constricted kidney while these parameters increased in the other kidney. After release of the constriction RPF (122±21 to 159±25 ml/min), FeNa (0.5±0.1 to 5.2± 1.2%), UNcAMP (187±119 to 837±185 pmol/min, $p<0.01$) and RVNcAMP (378±24 to 2010±470 pmol/min, $p<0.02$) rose significantly. In group II, FeNa, UNcAMP and RVNcAMP increased during VE and remained significantly elevated during the reduction in RPP. The data show that: 1) prevention of the exposure of the kidney to the hemodynamic effects of VE abolished both the natriuresis and the increased production of NcAMP, 2) once the kidney is exposed to the vasodilatation of VE the changes in FeNa and NcAMP are not reversed even if RPP is reduced, and 3) renal vasodilatation at normal RPP is the main factor responsible for the rise in NcAMP during VE.

● ON THE ROLE OF EXTRACELLULAR Ca^{2+} IN ADH EFFECT ON WATER PERMEABILITY OF TOAD BLADDER. Marcos A. Hardy & Donald R. DiBona*. Univ. of Miami Med. Sch., Miami, Fla., and *Univ. of Alabama Med. Ctr., Birmingham, Ala.

This report reexamines the dependency upon extracellular Ca^{2+} of the effects of ADH on the osmotic (Pos) and diffusional (P_w) permeabilities to water in toad urinary bladder. To avoid tissue disruption Ca^{2+} was removed from the serosal bath only and, in the absence of ADH, this produced no change in Pos, P_w, inulin permeability (Pin) or epithelial structure. With ADH (20mU/ml) the increase in Pos was inhibited while that of P_w was not and Pin remained low.

	Pos	Pw	Pin
	cm sec^{-1} x 10^4		cm sec^{-1} x 10^7
Control	167±6	3.4±0.1	1.0±0.3
Ca^{2+}-free	56±3	3.4±0.1	1.9±0.5
(n),p	(33),<.001	(11),>.5	(7),>.02

Microscopy revealed detachments of up to 100μm of granular (G) and mitochondria-rich (MR) cells from the basal cells and supporting tissues. G and MR cells remained interconnected with integrity of tight junctions. Measurements of Pos in glutaraldehyde-fixed bladders showed no effect of serosal Ca^{2+} withdrawal in bladders fixed without osmotic gradient and a 68% inhibition if prior to fixation a volume water flow develops. We conclude: 1) The serosal Ca^{2+}-requirement for ADH to increase P_w is very little, if any; 2) ADH-induced volume water flow across Ca^{2+}-deprived tissues induces structural modifications which lead to the inhibition of Pos, water being retained within the tissue; 3) In the absence of serosal Ca^{2+} the ADH-sensitive osmotic and diffusional water pathways are at least partially dissociated.

RENAL INTERSTITIAL PRESSURE AND SODIUM EXCRETION DURING BRADYKININ-INDUCED VASODILATION. Dale A. Hartupee*, John C. Burnett, Jr.*, Jim I. Mertz*, and Franklyn G. Knox, Dept. of Physiol. & Biophysics, Mayo Clinic, Rochester, MN 55901

An increase in renal interstitial pressure (RIP) has been proposed as a mechanism for the natriuresis caused by vasodilators. We investigated the relationship between RIP and sodium excretion during intrarenal bradykinin infusion (0.75 μg/min/kg). Decapsulation was employed to dissociate vasodilation from the increase in RIP. RIP and renal blood flow (RBF) were measured and clearances performed before and during bradykinin infusion in the presence and absence of the renal capsule in the same dog. When the renal capsule was intact, bradykinin significantly increased RIP, fractional sodium excretion (FE_{Na}), and RBF. Removal of the capsule blunted the bradykinin-induced increase in RIP without attenuating the increases in FE_{Na} or RBF. The changes in RIP, FE_{Na}, and RBF with bradykinin before and after decapsulation are:

	ΔRIP (mmHg)	ΔFE_{Na} (%)	ΔRBF (ml/min)
(n=5)			
control	15.9±1.7	1.66±0.50	50.8±12.7
decapsulated	5.8±2.1*	3.08±0.86	57.4±18.0

*$p<0.001$ compared to control response

In time control dogs without decapsulation, two consecutive infusions of bradykinin resulted in similar increases in RIP, FE_{Na}, and RBF for both infusions. The results are the first to demonstrate that bradykinin increases renal interstitial pressure and, further, that the natriuresis that occurs with bradykinin infusion can occur independently from changes in renal interstitial pressure.

DOPAMINE DECREASES FLUID REABSORPTION IN STRAIGHT PORTIONS OF RABBIT PROXIMAL TUBULE. Yoshihito Higashi* and Elsa Bello-Reuss, (int. by Mabel Purkerson). Dept. of Med., Jewish Hosp. of St. Louis and Dept. of Physiol. and Biophys., Wash. Univ., St. Louis, Missouri.

The diuretic and natriuretic effects of Dopamine (D), seen at doses that do not change RBF or GFR, suggest a direct action on the renal tubule. The effects of D and D-blockers on fluid transport and transepithelial potential (V_l) were studied in straight portions of the rabbit proximal tubule (PR) by the technique of microperfusion in vitro.

D (10^{-6}M) added to the bath (rabbit serum) produced a significant decrease in J_v ($nl \cdot min^{-1} \cdot mm^{-1}$) from 0.51 ± 0.14 to 0.26 ± 0.14 (n=5, $p<.002$). When perfusate and bath were identical artificial solutions, J_v values were: 0.34 ± 0.04 (control) and 0.21 ± 0.03 (D) ($p<0.01$). V_l decreased from -1.31 ± 0.71 to -0.32 ± 0.43 mV ($p<0.01$). Active drugs on D-receptors were used to characterize the action of dopamine. Haloperidol (10^{-8}M) did not modify J_v or V_l, but prevented the action of dopamine. Metoclopramide (10^{-6}M) exhibited an agonist effect: J_v decreased from 0.24 ± 0.05 to 0.14 ± 0.02 (n=4, $p<0.05$). Lisuride (L) 1.5 x 10^{-9}M, prevented the effect of D (J_v: 0.24 ± 0.02, 0.20 ± 0.02 and 0.23 ± 0.04 during control, L, and L + D respectively). It is concluded that D exerts a direct inhibitory effect on fluid transport by the PR. The pharmacological properties of the PR dopamine receptor are similar to those of D_1 receptors.

DOWN-REGULATION OF ADH-INDUCED NaCl ABSORPTION IN MEDULLARY THICK ASCENDING LIMBS. S. C. Hebert,* R. M. Culpepper,* and T. E. Andreoli.* Univ. of Texas Med. Sch., Depts. of Medicine & Physiology, Houston, Texas.

We have previously shown (Clin. Res. 28:533A, 1980), in isolated mouse medullary thick ascending limbs (mTALH), that ADH enhances net NaCl absorption (J^{net}_{NaCl}, pM sec^{-1} cm^{-2}) by increasing conservative, transcellular electroneutral NaCl transport, τ_{NaCl} (pM sec^{-1} cm^{-2}). The present studies examined effects of peritubular hypertonicity on ADH-stimulated NaCl transport in mTALH. Addition of 600 mM bath urea, in the presence of ADH (10 μU/ml), did not alter relative (P_{Na}/P_{Cl}=1.8 ± 0.02) or absolute (P_{Na}=0.22 ± 0.2 μm sec^{-1}) ionic permeability properties or cell volume, but did result in an 85% decrease in the ADH-dependent spontaneous transepithelial voltage (V_e, mV), J^{net}_{NaCl} and τ_{NaCl}. Urea bath hypertonicity also inhibited by 85% the 8-bromo-cAMP stimulated V_e in mTALH. These urea-mediated reductions in V_e were not reversed by supramaximal concentrations of either ADH or cAMP. Bath mannitol, 600 mM, decreased ADH-dependent V_e and reduced cell volume. Increasing peritubular NaCl to 290 mM reduced ADH-dependent J^{net}_{NaCl} by 80% due to a 47% fall in τ_{NaCl} and a 33% increase in bath to lumen NaCl backflux; cell volume was reduced. Thus in mTALH, ADH- and cAMP-mediated increases in τ_{NaCl} are offset by increased bath to lumen NaCl backflux, when peritubular NaCl concentrations rise; and by a non-competitive negative feedback reduction in τ_{NaCl} produced by increasing peritubular osmolality. Consequently, ADH may increase urinary concentrating power without affecting external NaCl balance.

EVIDENCE FOR A ROLE OF CELLULAR CALCIUM (Ca) UPTAKE IN THE NONOSMOTIC RELEASE OF ARGININE VASOPRESSIN (AVP) IN THE CONSCIOUS RAT. S. Ishikawa,* W. Handelman,* R. Schrier, and T. Berl (intr. by K. Duchin). Dept. Med., Univ. Colo. Hlth. Sci. Ctr., Denver, CO.

In vitro studies have suggested that Ca concentration in the bathing medium is essential for AVP release. The present in vivo experiments were undertaken to investigate the role of cellular Ca uptake in osmotic and nonosmotic release of AVP in conscious hydrated rats. Experimental rats were infused with IV verapamil (Ver; 50 μg/kg/min), a blocker of cellular Ca uptake, while control (C) rats were infused with normal saline. The antidiuresis following the infusion of 3% NaCl (2 ml/100 g body wt) was not different in these groups, as peak urinary osmolality (Uosm) was 819 in Ver-treated (n=6) and 672 mOsm/kg H_2O in C rats (n=6). In contrast, nonosmotic stimulation of AVP release with IP 6% dextran (1.8 ml/100 g body wt) resulted in a mean peak Uosm of 1069 in C (n=14) but only 476 mOsm/kg H_2O in Ver-treated rats (n=14, $p<.001$) in spite of a comparable decrease in blood volume. Similar results during IP dextran were obtained with a chemically dissimilar blocker of cellular Ca uptake, nifedipine (7.5 μg/kg/min). In these studies, following IP dextran peak Uosm rose to only 504 (n=6) as compared to the control value of 1069 mOsm/kg H_2O ($p<.001$). During IP dextran plasma AVP levels in 7 Ver-treated rats only rose to 4.3 pg/ml, a value significantly lower than the plasma AVP level of 12.8 pg/ml in 7 C rats ($p<.001$). These results therefore indicate that cellular Ca uptake plays an important role in modulating nonosmotic release of AVP in conscious rats.

THE STOP-FLOW PRESSURE MEASUREMENT OVERESTIMATES THE GLOMERULAR CAPILLARY HYDRAULIC PRESSURE (P_{GC}). Iekuni Ichikawa & Julia L. Troy*. Harvard Medical School, Boston, MA.

The stop-flow technique has been used widely for the estimation of P_{GC}. In this approach, P_{GC} is assumed to be perfectly autoregulated by the adjustments of afferent and/or efferent arteriolar vascular tones in response to stopped flow. To test the validity of this assumption, P_{GC} was measured in 7 hydropenic Munich-Wistar rats by direct micropuncture of superficial glomeruli under both stop-flow [$P_{GC}(D)_{sf}$] and free-flow [$P_{GC}(D)_{ff}$] conditions, and the results were compared with estimates obtained by stop-flow [$P_{GC}(SF)$] in the same nephrons. In contrast to previous studies by others, Bowman's capsules and early proximal tubules were not micropunctured before $P_{GC}(SF)$ or $P_{GC}(D)_{sf}$ measurements to avoid leakage of filtrate during stopped flow, which we found led to systematic underestimation of $P_{GC}(SF)$ and $P_{GC}(D)_{sf}$.

When this leakage was avoided, $P_{GC}(SF)$ averaged substantially higher than $P_{GC}(D)_{ff}$(53.7±3.0 mmHg vs. 44.4±2.7, $p<0.01$). However, $P_{GC}(SF)$ essentially equalled $P_{GC}(D)_{sf}$(53.5±3.0 mmHg), indicating that P_{GC} rises substantially during stopped flow presumably due to imperfect autoregulatory adjustments. Moreover, cessation of distal delivery alone did not alter $P_{GC}(D)_{ff}$(45.1±3.0 mmHg vs. 44.4±2.7), suggesting that the stop-flow-induced elevation in P_{GC} is a consequence of the mechanical obstruction upstream to the blockade rather than alteration in distal salt delivery (i.e. tubuloglomerular feedback). These results seriously question the validity of $P_{GC}(SF)$ as a reliable index for P_{GC}.

GLOMERULAR (G) AND TUBULAR (T) DOPAMINE (D) RECEPORS (R); EFFECT OF SODIUM INTAKE. P.Jose, R. Felder*, L. Schoelkopf*, J. Pelayo*, M.Blecher*, P. Calcagno and G. Eisner. Depts. of Peds, Biochem, Med, and Physiol and Biophys. Georgetown Univ. Med. Ctr., Wash. D.C.

D may play a role in the diuresis associated with an acute or chronic sodium load. We therefore examined G and T of rats for presence of DR. G and T were obtained by sieving. Dissociation constant (K_d) and receptor occupancy (R_o) for DR were determined using the ligand ^{3}H-haloperidol and the dopamine antagonist cis-flupenthixol. Binding was rapid reaching equilibrium in 5 minutes. Specific binding averaged 70%. Binding sites were saturable and stereospecific. Under unrestricted salt intake R_o in G (n=6) of 0.24±0.10 pmol/mg protein was significantly less than the R_o in T (n=6) of 1.24±0.49. K_d in G (n=6) of 6.98±1.51 nM was significantly less than the K_d in T (n=6) of 30.70±7.29. Additional studies were performed in rats on a varied salt intake in which sodium excretions were measured. Rats excreting greater than 1000 uEq Na/100 BW/24 hrs (n=5) had an R_o for G & T of 0.698±0.15 and 1.372±0.25 pmol/mg protein respectively. Rats excreting less than 1000 uEq Na/100 BW/24 hrs (n=4) had an R_o for G & T of 0.290±0.08 and 0.517±0.14 pmol/mg protein respectively. The rise in R_o in T with increased Na intake was significant ($p<.05$). Increasing Na excretion was associated with increased beta adrenergic receptors (BAR) in G (n=8, r=0.76) but not in T. Alpha adrenergic receptor (AAR) occupancies were not affected by sodium excretion. Variations in sodium excretion had no effect on K_d of DR, BAR or AAR. These studies are consistent with a role of DR and BAR in renal regulation of Na excretion.

ALDOSTERONE INCREASES Na^+ TRANSPORT IN CULTURED CELLS WITHOUT A CHANGE IN CITRATE SYNTHASE ACTIVITY. J.P. Johnson and S.W. Green*, Dept of Nephrology, WRAIR, Washington, D.C.

Aldosterone (A) increases citrate synthase (CS) activity in toad urinary bladder and rat kidney. It has been suggested that this action is important to A stimulation of Na^+ transport and has been used as a marker of those epithelia which are stimulated by A. We have studied the effect of A on CS in cultured epithelial cells of two cell lines (TB-M and TB-6C) derived from toad urinary bladder. In culture, these cells form oriented epithelia, actively transport Na^+ and respond to A with an increase in active Na^+ transport. Time course and concentration dependence of the response to A in cultured cells are similar to that of the intact bladder. CS synthase activities in sonicates of mitochondrial preparations from both cell lines and from intact toad urinary bladder were determined by the method of Srere et al. Eighteen-hour incubation of intact toad urinary bladder with 10^{-7}M A resulted in an increase in CS activity (nmol/min/mg prot) from 304 ± 24 to 422 ± 46 ($p < 0.025$). Eighteen-hour incubation of cultured cells with 10^{-7}M A resulted in no differences between control and A treated cells in either cell line (138 ± 5 to 131 ± 7.8 in TB-M and 102 ± 6 to 106 ± 3.9 in TB-6C). In cultured toad urinary bladder epithelial cells, A induces an increase in active Na^+ transport similar to that seen in intact bladder but does not increase the activity of CS. Therefore, in cultured cells at least, CS is not a critical enzyme for the stimulation of Na^+ transport by A nor would it be a suitable marker for epithelial cells affected by A.

MECHANISM OF URATE TRANSPORT IN DOG RENAL CORTICAL MICROVILLUS MEMBRANE VESSICLES (MMV). Andrew M. Kahn*, Peter S. Aronson, (Introduced by John A. Goffinet). Yale Univ. Sch. of Med., Depts. of Med and Phys., New Haven, Ct.

Uphill urate transport into dog renal MMV occurs from imposing an inwardly directed proton gradient (J.C.I. 65:931,1980). We seek to characterize further this transport process. MMV were isolated from the mongrel dog renal cortex by a Mg-aggregation method. The values for 10 sec uptake of .06-.73 mM urate at 20°C in the presence of a proton gradient (pH_o=6.5, pH_i=7.5) were determined by a Millipore filtration technique. Eadie-Hofstee analysis revealed only one transport site with a Km of 0.4 mM and a Vmax of 4.0 nmoles/min/mg protein. The 10 sec uptake of .06 mM urate was then measured in incubation media containing 50 mM Na^+, K^+, Li^+, Rb^+ or Cs^+, with (pH_o=6.5,pH_i=7.5) or without (pH= pH_i=7.5) a proton gradient. Under either condition there was no difference in urate uptake among the different cations. In the presence of an inwardly directed proton gradient, the 10 sec uptake of .06 mM urate was inhibited 74,76 and 75% by 1 mM SITS, DIDS and probenecid, respectively. The transport of PAH showed similar characteristics with respect to proton gradient stimulation, inhibitors, and cation dependence. We conclude that proton gradient-stimulated urate transport in dog renal MMV occurs via a single transport system, likely representing urate-OH^- exchange or H^+-urate contransport. This system is probably shared by PAH and is inhibited by SITS and DIDS as well as by prbenecid. In addition, there is no evidence for cotransport of urate or PAH with monovalent metal cations.

ALDOSTERONE BINDING ALONG THE RABBIT NEPHRON. Adrian I. Katz and Alain Doucet*, Department of Medicine, University of Chicago, Chicago, IL.

To identify the site(s) of mineralocorticoid action along the nephron, we measured the specific binding of [^{3}H]aldosterone ([^{3}H]A) to nephron segments microdissected from aldosterone-deficient rabbits. Tubules were incubated for 60 min. at 25°C in 1 µl of medium containing 6 x 10^{-9} M [^{3}H]A. Specific binding was defined as the difference between binding measured in the absence and in the presence of 2000-fold excess of unlabeled hormone, and is expressed as 10^{-18} mol. cm^{-1} ± SE. High specific binding capacity was found in the connecting tubule (108 ± 4), the cortical collecting tubule (CCT) (119 ± 9), and the medullary collecting tubule (115 ± 16), whereas specific binding was negligible in the proximal convoluted tubule (8 ± 9), pars recta (2 ± 6), medullary thick ascending limb (4 ± 6), cortical thick ascending limb (6 ± 2), and the distal convoluted tubule (6 ± 6). In CCT, a Scatchard analysis of the specific [^{3}H]A binding indicated a dissociation constant (K_d) of 2.2 x 10^{-9} M, and a maximal number of binding sites of 157 x 10^{-18} mol. cm^{-1}. Specificity was assessed from the displacement of [^{3}H]A binding by various steroids. CCT receptors revealed the following sequence of affinities: Aldosterone ≥ DOCA ≥ spironolactone > dexamethasone >> dihydrotestosterone, which suggests that they are mineralocorticoid receptors.

In conclusion, significant [^{3}H]aldosterone binding to receptors of high affinity and mineralocorticoid specificity was demonstrated only in the collecting tubule, suggesting that this nephron segment is the target site for mineralocorticoid action in the rabbit kidney.

POTASSIUM REABSORPTION IN ISOLATED PROXIMAL CONVOLUTED TUBULE. J.S. Kaufman, C. Lechene and R.J. Hamburger. Boston VA Medical Center and Harvard Medical School, Boston, MA.

Potassium reabsorption in the proximal tubule is thought to be closely related to fluid reabsorption, although no detailed investigation of this relationship has been performed. We sought to further define this association using the technique of isolated perfused tubule microperfusion. Proximal convoluted tubules from New Zealand white rabbits were perfused using standard techniques. Perfusate and bath both contained potassium at a concentration of 4 mM. The perfusion rate was varied from 2.7 to 21.7 nl/min. Potassium concentrations in perfused and collected samples were determined by electron probe microanalysis. In 10 tubules there was no clear relationship between perfusion rate and potassium flux. However, there was a direct linear correlation between water reabsorption and potassium reabsorption (J_K=3.13 J_v-2.69, $p<0.01$). This finding suggests that potassium reabsorption is in some way coupled to water and/or sodium reabsorption in the proximal convoluted tubule.

RENAL VASCULAR RESPONSES TO HYPERTONIC SOLUTIONS INCLUDING ROENTGEN CONTRAST AGENTS. Richard W. Katzberg,* Leonard G. Meggs,* and Norman K. Hollenberg. Harvard Medical School, Dept. of Radiology & Medicine, Boston, Massachusetts.

Hypertonic solutions, including roentgen contrast media, induce vasodilatation in all vascular beds: in the special case of the kidney the initial vasodilatation is followed by a pronounced, secondary fall in renal blood flow, which has been attributed to renin release. We performed two groups of studies on the renal blood flow (flowmeter) in six anesthetized dogs. To assess the role of renin release, the flow response to 4 ccs of meglumine/sodium diatrizoate-76% was assessed before and during infusion saralasin (.33-.76 µg/kg/min, i.a.): saralasin did not prevent the flow reduction (-22±8.7 vs. -34±8.9 ml/min). To assess whether filtration was required to reduce RBF we compared the flow response to 4 ml of isosmolal dextran (mw 70,000) and mannitol (mw 182). Mannitol induced the typical biphasic response: an initial increase followed by a fall (-10±2 ml/min). Dextran resulted in only an increase in RBF. We conclude that angiotensin is not involved in the secondary blood flow fall by hypertonic solutions which is unique to the kidney. The difference between mannitol and dextran raises the possibility of a mechanical rather than hormonal mechanism for the flow reduction.

ANION TRANSPORT REGULATES CELL pH IN PROXIMAL TUBULES: J. Kleinman, R. Ware,* and J. Schwartz, Departments of Medicine, VA Medical Center and the Medical College of Wisconsin, Milwaukee, WI and Boston University School of Medicine, Boston, MA.

The regulation of cell pH (pHc) by anion transport was examined in suspensions of rabbit renal proximal tubules. pHc was derived from ^{14}C-DMO distribution. In buffer with 10mM/L HCO_3^- and gassed with 5% CO_2, the anion transport inhibitors, SITS and furosemide, raised the cell-to-extracellular pH gradient (ΔpH) from 0.23±0.02 to 0.31±0.02 and 0.31±0.03, respectively, but in combination their effects were not additive. Replacement of extracellular Cl^- by NO_3^- raised ΔpH from 0.24±0.04 to 0.37±0.05. Neither SITS nor furosemide raised ΔpH in Cl^--free media. SITS raised steady-state cell-to-extracellular $^{36}Cl^-$ distribution from 0.31±0.05 to 0.41±0.04. Furosemide had a similar effect, raising the distribution from 0.18±0.04 to 0.28±0.04. Incubation of suspensions in HCO_3^- and CO_2-free media raised ΔpH from 0.18±0.02 to 0.29±0.03. Removal of Cl^- in addition to HCO_3^- and CO_2, raised pHc still further, to 0.36±0.02. The results demonstrate that two different anion transport inhibitors raise pHc and ΔpH in proximal tubules and are consistent with the idea that the mechanism for this effect is inhibition of alkali anion exit from the tubule cell. This process appears to depend on extracellular Cl^- and probably occurs primarily by HCO_3^- transport. The results support the concept that alkali anion transport, in the form of HCO_3^- exit from the cell, is an important regulator of cell pH in renal proximal tubule.

OXALATE SECRETION IN THE RAT PROXIMAL TUBULE. T. F. Knight, S. C. Sansom,* H. O. Senekjian, and E. J. Weinman. VA Medical Center and Baylor College of Medicine, Houston, Texas.

Simultaneous peritubular capillary and luminal microperfusion studies were performed to examine the secretory characteristics of the organic acid oxalate in the proximal convoluted tubule. Increases in oxalate concentration in the peritubular capillary perfusion solution from 0.096 to 4.3 mM resulted in progressively higher rates of oxalate secretion. As oxalate concentration in the peritubular capillary perfusate was increased further to 9.6 mM, there was a tendency for the secretory rate to plateau. Addition of para-chloromercuribenzoate, sodium cyanide, indanyloxyacetic acid, furosemide, or para-aminohippurate significantly decreased the secretory flux of oxalate. Probenecid in a concentration of 10^{-4} M inhibited oxalate secretion when the oxalate concentration in the peritubular capillary perfusate was 1.1 and 4.3 mM, but did not affect oxalate secretion at higher peritubular capillary concentrations of oxalate.

These studies indicate that oxalate secretion in the proximal convoluted tubule is an active, carrier-mediated process. Estimation of the apparent transport constants reveal it to be a low-affinity (Km 5.35 mM), high-capacity (Vmax 15.33 pmol/min/mm) secretory system. This secretory system is also capable of transporting other organic acid compounds. Taken together with data from previous studies examining oxalate, in which probenecid had no effect on oxalate secretion, these studies suggest that more than one oxalate secretory system exists in the proximal convoluted tubule.

EFFECTS OF TRIFLUOPERAZINE (STELAZINE, TFP) ON FUNCTION AND STRUCTURE OF VASOPRESSIN-TREATED TOAD URINARY BLADDER. S.D. Levine, W.A. Kachadorian, D.N. Levin, D. Schlondorff. Dept. Medicine, Albert Einstein Coll. Medicine, Bronx, NY and Renal Service, USPHS Hosp., Staten Island, NY.

In order to evaluate the role of calcium in vasopressin-stimulated transport, we examined the effect of TFP, a compound which binds specifically to the calcium binding protein calmodulin and thereby inhibits processes dependent on the calcium-calmodulin complex. 10μM TFP reversibly inhibited vasopressin-stimulation of water flow by 50%, but did not affect urea or sucrose permeability or short-circuit current. TFP also blocked stimulation of water flow by cyclic AMP and methylisobutylxanthine, implying a "post-cyclic AMP" site of action. Consistent with these results, TFP did not alter epithelial cyclic AMP content or the cyclic AMP-dependent protein kinase activity ratio (-cAMP/+cAMP). Assay of bladder epithelial cell supernatant demonstrated calmodulin-like activity of 1.5U/μg protein. Morphologic studies of vasopressin-treated bladders revealed that TFP decreased the frequency of luminal membrane aggregates, structures which are accurate markers of luminal membrane water permeability, by 60%. In contrast, TFP had no effect on microtubules and did not significantly decrease the number of fusions between cytoplasmic, aggregate-containing membranes and the luminal membrane. TFP thus appears to inhibit the movement of preformed particle aggregates from the fused intracellular membranes to the luminal membrane, perhaps by blocking an effect of calcium on microfilament function.

MEASUREMENT OF THE LIQUID JUNCTION POTENTIALS INVOLVED IN THE DETERMINATION OF PROXIMAL TUBULE TRANSEPITHELIAL POTENTIALS. Raynald Laprade*, Jean Cardinal. Centre de Recherche, Hôpital Maisonneuve-Rosemont and Depts. of Physics and Medicine, Univ. de Montréal, Montréal, Québec, Canada.

Transepithelial potential difference (TPD) measurements in the isolated proximal tubule always involve the presence of liquid junction potentials (LJP) between perfusate (P) and bath (B) solutions or between these and the electrodes, if B differs from P. These LJP must be corrected for in order to determine the driving force for ions and solutes transport. Attempts to evaluate these LJP using Henderson's equation or measurements with saturated KCl electrodes have been most often unsatisfactory. We have therefore designed a method of measurement, using AgAgCl electrodes and a liquid junction formed across the tip of a micropipet. The potential difference measured is the LJP plus the difference between the two electrode potentials (EPD). This EPD is calculated from the measured Cl ion concentrations, correcting for the Cl activity coefficient, considering, in presence of proteins, Cl binding and protein volume. Mean values of LJP at 39°C with control solutions for B-P, P-Na, and B-Na junctions (where Na = 154 mM NaCl and B contains 6 g/100 ml albumin) are 2.3, 1.7, and 4.0 mV, respectively, measured relative to the first solution. These values are about 40% higher than those measured using a saturated KCl electrode. Since uncorrected values of TPD measured for proximal convoluted and straight tubules with similar artificial solutions vary between 1.5 and 3 mV (lumen negative), the actual TPD is therefore negligible or positive even in the absence of an imposed Cl gradient.

RECENT PROGRESS IN PURIFICATION OF NATRIURETIC FACTOR(NF). A. Licht, S. Stein*, R.L. Bowman* and N.S. Bricker. Nephrology Division, UCLA School of Medicine, Los Angeles, CA, and Roche Institute of Molecular Biology, Nutley, N.J.

The standard technique we have employed in our efforts to isolate and identify the NF involved 5 separate chromatographic steps. Urine of normal dogs after "escape" from 250 mEq Na diet and fludrocortisone and urine from uremic patients were used. With each step in purification biologic activity was lost, making final identification of the active product more difficult. Hence a shorter and simpler technique was required in order to obtain larger quantities of more potent and equally pure material. Desalting of 72 hr batches of urine was performed on 12 x 110 cm Sephadex G-25 columns. A "post-salt" fraction containing the biologic activity was then subjected directly to reverse phase high performance liquid chromatography on RP-18 (Altex) resin. The column eluate was stream sampled and the fluorescence was automatically monitored using fluorescamine. The eluate from 20 to 43 minutes was divided into 5 fractions and each was tested for biologic activity using the remnant rat assay. Urinary sodium excretion ($U_{Na}V$, μEq/min) and fractional excretion of sodium (FE%) were compared before and after IV infusion of the fraction. One narrow fraction with elution time of 25-28 min. consistently exhibited potent NF activity ($\Delta U_{Na}V$= 1.88±0.10, and ΔFE_{Na} 2.24±0.13; n=5). The other 4 fractions had no significant natriuretic effect. The final product with this technique has 5 times more activity than with the previous process. The opportunity to harvest a narrow fraction of eluate with high potency in large quantities should enhance the chances of definite isolation of NF.

EARLY EFFECT OF TRIIODOTHYRONINE ON RENAL HANDLING OF POTASSIUM AND SODIUM IN THE RAT. Chu-Shek Lo and Dan Gerendasy*. Uniformed Services University, Dept. of Physiology, Bethesda, MD 20014

The early effect of triiodothyronine (T_3) on renal handling of K^+ and Na^+ in hypothyroid and euthyroid rats was studied. One injection of T_3 was administered to hypothyroid and euthyroid rats. The individual rats were kept in metabolic cages. Sodium and potassium intake as well as urinary Na^+/K^+ ratio and excretion were determined daily for the first two days after injection. Compared to euthyroid rats, the intake and excretion of K^+ over the 24 h immediately prior to T_3 injection were 15% ($P<.005$) and 31% ($P<.001$) less, respectively, in the hypothyroid rats. In the first two days following one T_3 injection, K^+ intake and urinary K^+ excretion showed no change in either group of rats. As compared with the euthyroid rats, Na^+ intake and urinary Na^+ excretion over the 24 h immediately prior to T_3 injection were 12% ($P<.05$) and 14% ($P<.05$) lower, respectively, in the hypothyroid rats. Na^+ intake and urinary Na^+ excretion showed no significant changes in the first 2 days after T_3 injection in either group. It is well established that increased aldosterone secretion could lead to a decrease in Na^+ excretion and an increase in K^+ excretion. Before injecting T_3 the urinary Na^+/K^+ ratio in hypothyroid rats was 48% higher than that in euthyroid rats, and remained unchanged in both groups at 24 and 48 h after injection. Since our results showed no differences in Na^+ excretion, K^+ excretion and urinary Na^+/K^+ ratio at 24 and 48 h after one injection of T_3, in the hypothyroid and euthyroid rats respectively, the absence of an early response of aldosterone secretion to T_3 is implied.

● INFLUENCE OF CHARGE ON FERRITIN UPTAKE IN THE NEPHRON. K.M. Madsen,* R.H. Harris, and C.C. Tisher. Duke Univ. Med. Center, Durham, N.C. and University of Florida, Gainesville, FL.

The uptake and intracellular distribution of anionic ferritin (AF) and cationic ferritin (CF) were studied in the proximal and distal convoluted tubule of rat kidney. Male Sprague-Dawley rats were prepared for micropuncture and single proximal and distal tubules were perfused with AF (5-20 mg/ml) or CF (0.1-2.0 mg/ml) in isotonic saline for 3 min. Either immediately or 60 min after ferritin exposure, the tubules were fixed by perfusion with 6.25% glutaraldehyde. Electron microscopy of proximal tubules fixed after 3 min of perfusion with ferritin revealed that CF was bound to the apical cell membrane and located in large amounts in endocytic vacuoles. AF was also located in endocytic vacuoles, but binding to the apical cell membrane was not observed. Sixty min after perfusion with ferritin, both AF and CF were located primarily in lysosomes. Ferritin was not observed in the Golgi cisternae. The uptake of CF in the proximal tubule was considerably greater than that of AF. Electron microscopy of distal tubules fixed after 3 min of perfusion with ferritin showed extensive binding of CF to the apical cell membrane and localization in intracellular vacuoles. AF was not bound to the apical cell membrane and very little was present in intracellular vacuoles. These results demonstrate that CF is bound to the negatively charged apical cell membrane of both proximal and distal convoluted tubules and that the tubular uptake of CF exceeds that of AF, indicating that the charge of a protein molecule may play an important role in the binding and uptake of the protein into both proximal and distal tubules.

● EFFECT OF QUINIDINE ON cAMP-INDUCED CHANGES IN HYDRAULIC CONDUCTANCE (L_p) OF ISOLATED PERFUSED COLLECTING TUBULES OF THE RABBIT. M. Lorenzen* E.E. Windhager and A. Taylor. Dept. of Physiology, Cornell Univ. Med. Coll., New York, N.Y.

Quinidine, a drug thought to increase cytosolic calcium levels, has been found to inhibit the hydro-osmotic response to vasopressin and cAMP in the toad bladder (A. Taylor, Fed. Proc. 34:285, 1975). To test whether quinidine has a similar effect in the mammalian nephron, experiments were carried out on isolated perfused rabbit collecting tubules. Tubules were perfused at 37°C with dilute phosphate buffered Ringer's solution (140 mOsm /kg H_2O) and bathed in bicarbonate buffered Ringer's (290 mOsm/kg H_2O at pH 7.5). Cl-PheS-cAMP was added to the bath at 10^{-4}M in control and experimental conditions. Quinidine added to the bath in the range 10^{-6} to 10^{-4}M had no effect on baseline L_p; for example, with 10^{-4}M quinidine, basal L_p ($\times 10^{-7}$ cm · sec^{-1} atm^{-1}) was 25.7 ± 2.9, while in the paired controls L_p averaged 25.9 ± 13.6 (n=4; N.S.). After quinidine at 10^{-6}, 5×10^{-6}, 5×10^{-5} and 10^{-4} M, cAMP-induced increases in L_p averaged 311 ± 34 (n=4), 222 ± 30 (n=5), 150 ± 18 (n=5) and 134 ± 26 (n=4) respectively; in the absence of quinidine, cAMP increased L_p by an average of 323 ± 22 (n=18). On a paired basis, inhibition by quinidine averaged 1 ± 9% (N.S.) at 10^{-6}M, 30 ± 6% ($p<0.005$) at 5×10^{-6}M, 53 ± 6% ($p<0.02$) at 5×10^{-5}M and 57 ± 5% ($p<0.03$) at 10^{-4}M. These results demonstrate that quinidine inhibits the hydro-osmotic response to cAMP in the mammalian collecting tubule in a dose-dependent manner. The findings are consistent with the notion that cAMP-induced changes in L_p are inhibited by an increase in cytosolic Ca ion activity.

● LOCALIZATION OF ALDOSTERONE-TARGET SITES IN RABBIT RENAL MEDULLA. D. Marver & W.E. Lombard (intr.by J. P. Kokko), U. Texas Hlth Sci Ctr, Dallas, Tx.

We have previously shown that rabbit renal cortex and outer medulla, but not papilla contain mineralocorticoid-specific cytoplasmic receptors. To identify nephron targets for aldosterone (ALDO) within these two zones, we have assayed segments for citrate synthase (CS), an enzyme induced by ALDO in target epithelia. (It is thought that CS induction is part of a cascade of events necessary to provide ATP for increased Na^+ reabsorption). Previous results on cortex showed that only the cortical collecting duct responded to ALDO as monitored by CS. We now examine the effect of adrenalectomy (ADX) and steroid replacement in medullary thick ascending limb (mTALH) and inner/outer stripe of medullary collecting duct (MCD_{is}, MCD_{os})

CITRATE SYNTHASE ACTIVITY (mol/kg dry wgt/hr, 28°C)

	ADX	ADX+ALDO*	ADX+DEX*	NORMAL
mTALH	9.5±0.7°	13.3±1.3	7.9±0.5	16.3±1.3
p vs ADX		<0.02	NS	<0.001
p vs NORM		NS	<0.001	
MCD_{os}	5.6±0.6	6.0±0.5		7.1±0.5
p vs ADX		NS		NS
MCD_{is}	3.5±0.2	5.4±0.5		5.0±0.4
p vs ADX		<0.002		<0.002
p vs NORM		NS		

*Rabbits sacrificed 90' post 10 µg/kg BW ALDO or dexamethasone (DEX); °±SEM. Rabbits/group=5 to 11. These studies indicate that ADX results in reduced CS activity in mTALH and MCD_{is}; and that acute administration of ALDO returns values to normal. In contrast, DEX does not elevate CS in mTALH's of ADX rabbits. Taken together with our results in cortex, these studies indicate a role for ALDO in the mTALH as well as the collecting duct system.

CIMETIDINE (C) SECRETION BY SUPERFICIAL PROXIMAL STRAIGHT TUBULES (SPST). T.D. McKinney, P. Myers* and K.V. Speeg, Jr.*. V.A. Med. Ctr. and Vanderbilt Univ. School of Medicine, Nashville, Tennessee.

C is a commonly prescribed drug whose major route of elimination is by urinary excretion. The present studies evaluated C transport by rabbit SPST perfused in vitro. Tritium labelled C added to the bath was actively secreted into the tubule lumen and reached a mean concentration 9 times that of the bath. Concentration differences as high as 26 were observed in some experiments. The rate of C secretion followed saturation kinetics characteristic of carrier mediated transport with a K_m of 102 x 10^{-6} M and V_{max} of 943 fmol mm^{-1} min^{-1}. Lumen to bath fluxes were only 11-18% of bath to lumen fluxes. High performance liquid chromatographic analysis showed that the chemical composition of C in tubular fluid was similar to that in the bath. C secretion was inhibited in a dose dependent fashion by quinidine, quinine, tolazoline, probenecid, phloridzin, creatinine, and cimetidine sulfoxide. At similar concentrations quinidine was the most potent inhibitor. With 10^{-4} M quinidine and 10^{-3} M quinine C secretion was virtually eliminated. C secretion was also reduced by hypothermia and ouabain. We conclude that C is actively secreted by rabbit SPST in vitro. C transport appears to occur by both the organic base and acid transport systems. The affinity of C is evidently greater for the base system. These studies raise the possibility of interaction of C with other drugs at the level of the renal tubule.

PROLINE TRANSPORT BY RENAL MEMBRANE VESICLES DERIVED FROM DOGS WITH SPONTANEOUS FANCONI SYNDROME. M.S. Medow*, R.A. Reynolds*, K.C. Bovee, and S. Segal Children's Hospital of Phila., Dept. of Pediatrics, and School of Veterinary Medicine, Univ. of Penna., Philadelphia, Pennsylvania

We have previously described the occurrence of spontaneous renal tubular defects in Basenji dogs, similar to idiopathic Fanconi syndrome. Clearance studies show the renal handling of glucose, $PO_4^{=}$, Na^+, K^+, uric acid and amino acids to be abnormal. Amino acid uptake by renal cortical slices reveals decreased uptake when compared to normal dogs. To further characterize the nature of this defect, the uptake of proline by renal luminal membrane vesicles from 2 affected, and 6 normal Basenji dogs was examined. Clearance studies show the fractional reabsorption of proline in the 2 dogs to be defective (74% and 89% vs. 98% in controls). The magnitude of the Na^+-dependent 0.02mM, 1 min proline uptake was 0.31 and 0.17nmoles/mg protein (controls=0.41±.04). Kinetic data from initial uptake (15 sec) of 0.0208-4.5008mM proline suggests a 2 component transport system. The high affinity system in the 2 affected dogs has apparent K_m's of 0.08 and 0.07mM, and V_{max}'s of 1.2 and 0.7nmoles/mg protein/15 sec(controls; K_m=0.08, V_{max}=2.0). The K_m's of the low affinity system are 2.6 and 1.6mM, with V_{max} values of 4.0 and 2.2nmoles/mg protein/15 sec(controls; K_m=0.65, V_{max}=5.7) While the high affinity system shows only a decreased velocity in the affected dogs, the low affinity system shows both a decreased affinity and velocity for proline transport. The data suggest that in this model of Fanconi syndrome, the defective renal reabsorption of proline may be explained in part by an alteration of luminal transport systems.

EFFECTS OF HYPOPROTEINEMIA ON JEJUNAL ABSORPTION IN PURINE AMINONUCLEOSIDE(PAN)NEPHROTIC RATS(N). M. McVicar, J. Mor, S. Teichberg, R. Wapnir. Dept of Peds, North Shore Univ Hosp, Manhasset, N.Y. and Dept of Peds, Cornell Univ Med College, NY, NY.

Effects of hypoproteinemia and edema were separated by performing jejunal perfusions in vivo 14 days after a single IV dose of PAN when N were still hypoproteinemic but no longer edematous. The mean serum albumin of N was 1.46 vs 2.63 for controls (C). Mean absorption (mM/min/cm ± SEM) of glucose at the physiologic concentration of 4 mM was 27.3 ± 0.3 in N vs 31.3 ± 1.16 in C ($p<0.005$). The absorption of glucose was also decreased in N at concentrations of 10, 20 and 40 mM and calculations of the kinetic constants resulted in a V_m of 81.0 ± 7.5 nmoles/min x cm for N vs 203.2 ± 59.2 nmoles/min x cm for C. The K_m for glucose was 6.5 ± 1.9 mM in N vs 25.1 ± 13.2 mM in C indicating that both the maximum rate of absorption as well as the affinity of the carrier mechanisms for glucose were decreased in N. Absorption of the non-metabolizable glucose analogue, 3-0-methylglucose was also decreased (N=10.6 ± .32 vs C=14.1 ± .45 $p<.001$) but absorption of fructose was normal at 4 and 10 mM. Absorption of phenylalanine (N=4.5 ± .19 vs C=5.3 ± .25, $p<.01$) histidine (N=4.6 ± .14 vs C=6.3 ± .16, $p<.001$), and glycine (N=4.4 ± .13 vs C=5.3 ± .16, $p<.001$) but not of lysine was decreased in N. The jejunal mucosa of N and C had similar enzyme activity for lactase, sucrase, maltase and Na-K ATPase. The ratio of RNA to DNA was also similar in the mucosa of N and C. The data suggests that the impaired jejunal transport is a result of intracellular protein depletion and impaired synthesis of active transport components in N.

● ROLE OF PAPILLARY UREA IN THE DEVELOPING CONCENTRATING ABILITY OF THE NEONATAL RAT. Dirk B. Mendel* and Brian R. Edwards. Dartmouth Medical School, Dept. of Physiology, Hanover, NH.

We previously reported a temporal relationship between elongation of superficial loops of Henle (SLH) and rising papillary (PAPosm), and urinary, osmolality in the dehydrated neonatal rat (Fed. Proc. 39:335, 1980). While the SLH were growing (up to ∿ 16 days), PAPosm increased at a rate of 26 mOsm/Kg H_2O · day. From 16 to 23d, after the SLH had maximally penetrated the outer medulla, PAPosm increased by 107 mOsm/Kg H_2O · day. We hypothesized that the more rapid rate of increase may be partially due to enhanced deposition of urea because of increased medullary recycling of urea consequent to the growth of the SLH. To test this hypothesis we have measured the ratio of urea to total solute concentrations in papillae of 91 rats (aged 4 to 65d) subjected to an 18h dehydration. The contribution of urea to papillary solute increased rapidly from 25% at 4d to 46% at 15d, with little further change. Plasma urea concentration in both dehydrated and normally hydrated rats was highest in the younger animals and declined slightly with age. Hence, the preferential accumulation of papillary urea during the first 15d is not due to increased circulating levels of urea. The pattern of the age-related change in relative contribution of urea to papillary solute was strikingly similar to the time-course of elongation of SLH determined in our previous study. This result lends further support to the hypothesis that elongation and functional maturation of the SLH promotes greater medullary recycling of urea leading to enhanced deposition of urea within the renal papilla.

DEFECTIVE RENAL DISTAL TUBULAR HYDROGEN SECRETION IN THE HYPOTHYROID RAT. U.F. Michael, L.A. Meeks,* and C.A. Vaamonde. Medical and Research Services, VAMC, Tucson, Arizona and Miami, Florida

We have previously demonstrated an inability of hypothyroid rats (HR) to acidify their urine normally during acid loading (Pflügers Archiv. 361:215,'76) and to generate urinary CO_2 tensions similar to their normal controls (CR) during bicarbonate loading (Clin. Res. 24:407A,'76). In order to assess whether this defect of distal hydrogen ion handling is due to a gradient limitation or due to a secretory impairment of hydrogen ion, HR and agematched CR received infusions of neutral phosphate at a rate of 0.03 $mM \cdot min^{-1} \cdot Kg^{-1}$. The provision of excess buffer in the distal nephron will bind secreted hydrogen ion and prevent its back diffusion. The means of the maximal $UPco_2$ obtained at UpH of 6.7-6.9 are reported: ($\bar{X}$±SE)

	BpH	$BPco_2$	UpH	$UPco_2$	U_P	U_PV
HR (n=5)	7.40±.02	38±1	6.75±.01	78±1	347±34	6.1±.7
CR (n=5)	7.41±.01	37±1	6.79±.02	105±5	398±59	4.4±.7
P	N.S.	N.S.	N.S.	<0.001	N.S.	N.S.

($BPco_2$ and $UPco_2$ [mmHg] = blood and urine CO_2 tension, U_P [$mg \cdot dl^{-1}$] = urinary concentration of phosphate; U_PV = [$mg \cdot min^{-1} \cdot Kg^{-1}$] = urinary excretion rate of phosphate.)

These data mitigate against a gradient limitation of hydrogen ion excretion and are best explained by a distal tubular defect of hydrogen ion secretion in the hypothyroid rat.

RENAL ANGIOTENSIN AND PROSTAGLANDIN INTERACTION IN SODIUM REPLETE AND SODIUM DEPLETE CONSCIOUS DOGS. K. Obeid,* E. Lianos,* C. Bentzel and R. Venuto. Department of Medicine, State University of New York at Buffalo, Buffalo, NY.

Five conscious dogs were studied while sodium replete (Na ↑) and in a chronic sodium deplete (Na ↓) state. Renal plasma flow (RPF ml/min ± SEM) was lower in Na ↓ state, 173.2 ± 42.7 vs. 268.3 ± 31.2 Na ↑ ($p < 0.01$). Glomerular filtration rate (GFR ml/min ± SEM) was also lower in dogs during Na ↓ 46.9 ± 5.6 vs. 58.6 ± 5.1 during Na ↑ ($p < 0.01$). Baseline plasma renin activity (Ng/ml/hr ± SEM) was 3.0 ± 0.5 during Na ↓ and 1.1 ± 0.3 during Na ↑. Infusion of a pressor dose of Angiotensin II (AII) decreased RPF in Na ↑ state to values comparable to those in the control period of the Na ↓ state. AII infusion in Na ↓ state reduced RPF and GFR to 88.3 ± 31.4 and 26.1 ± 4.7, respectively ($p < 0.001$).

Prostaglandin inhibition (PI) lowered RPF only in the Na ↓ state (135.4 ± 36.6) ($p < 0.02$).

The combination of AII and indomethacin decreased GFR and RPF in both volume states. This effect was more severe in Na deplete dogs. In this setting a reversible acute renal failure was produced (GFR 6.7 ± 1.8; RPF 29.6 ± 11.6).

We conclude:

1) AII infusion during Na ↑ reproduces the renal hemodynamics of the Na ↓ state; it appears that the vasoconstrictor effect of endogenous AII is a major determinant of RPF during Na ↓.

2) The importance of renal prostaglandins in the defense of renal hemodynamics during volume depletion is confirmed. This action appears to be related to a specific antagonism of AII.

A NEW METHOD OF MEASURING THE DETERMINANTS OF GFR. Leon Moore,* Stephen Weinstein, Enrique Pastoriza*. Dept. Physiol. & Dept. Nephrol., SUNY at Stony Brook, New York. (Introduced by L. Arbeit)

Current methods of determining the ultrafiltration coefficient (K_f) and glomerular plasma flow (GPF) require 8 measurements of tubular and vascular variables, which cannot usually be obtained from one nephron. We have developed a new means for estimating the determinants of GFR, which dispenses with the need for collecting efferent arteriolar blood and permits all measurements to be made in the same tubule. The method is based upon a mathematical model of GFR. The model predicts that, as the hydrostatic pressure difference across the glomerular capillary wall is diminished by raising proximal intratubular pressure (PITP), the driving force for filtration decreases in a predictable way, depending upon the prevailing values of K_f and GPF. The method requires at least 2 estimates of NGFR, one obtained at free-flow PITP and one at a PITP elevated by an immobile tubular block and a slowed rate of collection. Also needed are glomerular capillary pressure, systemic arterial blood pressure and protein concentration. Insertion of the data into the analytic solution of the model yields a system of non-linear, simultaneous equations, the solution of which gives unique values of K_f and GPF. To verify the procedure, measurements were obtained from 11 nephrons of 4 hydropenic, Sprague-Dawley rats, found not to be in filtration pressure equilibrium. The value of K_f obtained was 2.1 ± 0.3 (SEM) nl/min/mm Hg and of GPF was 106 ± 17 nl/min, which compares well with published values. Thus, this procedure provides a much-simplified, yet reliable method for studying glomerular filtration dynamics.

EFFECTS OF FUROSEMIDE ON MEMBRANE POTENTIALS AND INTRACELLULAR Cl^- ACTIVITY (Cl_c) IN EARLY DISTAL TUBULE OF AMPHIUMA. Hans Oberleithner,* William Guggino* and Gerhard Giebisch. Yale University School of Medicine, Department of Physiology, New Haven, CT.

Studies were performed in the doubly-perfused Amphiuma kidney which provides early distal tubule segments at the surface accessible to micropuncture techniques and offers cells large enough for cellular impalements with double-barreled Cl^--selective liquid ion exchange microelectrodes. In order to characterize the mechanisms responsible for Cl^--movement from lumen to the peritubular side, Cl_c, peritubular and transepithelial membrane potential difference (PD_{PT}, PD_{TE}) were measured under control conditions and with 10^{-4} M furosemide added to the luminal perfusion. Results: Control values of PD_{PT}, PD_{TE} and Cl_c are 75±1 mV (SEM), 10.2±0.8 mV (lumen positive) and 11.5±0.4 mM, respectively. This is consistent with Cl^- being above equilibrium across both membranes. After furosemide PD_{PT} hyperpolarizes within seconds to 86±1 mV in parallel with a rapid decrease of Cl_c^- to values of 3.3±0.4 mM. PD_{TE} decreases to 1.2±0.6 mV whereas almost no voltage change is observed across the luminal membrane. Luminal perfusion with Na^+-free solutions results in similar changes of the membrane potentials and Cl_c^-. Under both conditions the large electrochemical gradient for Cl^-, directed from cell to lumen, is abolished. Conclusion: Cl^- movement across the luminal cell membrane is electrically silent and is mediated by NaCl cotransport. This transport system is inhibited by furosemide. Peritubular hyperpolarization results from the fall in Cl_c^- and increase of rheogenic sodium extrusion.

EFFECTS OF DOCA IN K-DEPLETED RATS. Christopher W. Old*, Cristobal G. Duarte, and Michael Siedlecki*. Deptartments of Nephrology, Walter Reed Army Institute of Research and Uniformed Services University of the Health Sciences; Washington, D.C. and Bethesda, Maryland.

In order to determine the effect of DOCA in K-depletion, 12 rats were fed a control diet for 5 days (C rats) and then as they were switched to a K-deficient diet for 11 days, they were divided into 2 groups of 6 rats each: one was injected with 5 mg/Kg bw DOCA daily (Low K DOCA rats) while the other was injected with oil (Low K rats). There was no difference in water balance between C and Low K rats but it increased in Low K DOCA rats (C 14 ± 2, Low K DOCA 19 ± 0.7 ml/24 hr, $p < 0.01$). Na balance was higher in Low K DOCA rats (Low K + 1217 ± 573, Low K DOCA + 1313 ± 275, μEq/24 hr, p NSD) and K balance was more negative in DOCA treated rats (Low K - 113 ± 32, Low K DOCA - 370 ± 197 μEq/24 hr, p 0.05). The content of Na in muscle increased in Low K rats (C 152 ± 4, Low K 200 ± 0.5 μEq/gm, $p < 0.025$) and this effect was potentiated by DOCA (Low K DOCA 259 ± 6 μEq/gm, Low K - Low K DOCA $p < 0.025$). The content of K in muscle was lower in Low K rats (C 443 ± 15, Low K 367 ± 12 μEq/gm $p < 0.0025$) and decreased even further in DOCA treated animals (Low K DOCA 310 ± 9 μEq/gm, Low K - Low K DOCA $p < 0.0025$). Measurements of blood volume revealed no differences in red cell volume among the 3 groups but plasma volume was higher in Low K DOCA rats (C 31 ± 0.7, Low K 32 ± 0.8 ml/Kg, p NSD. Low K DOCA 39 ± 0.8 ml/Kg. Low K - Low K DOCA $p < 0.005$). This study demonstrates that DOCA exerts significant effects on Na, K and water balance and on tissue content of electrolytes in K-depleted rats.

● ISOLATED PERFUSION OF SINGLE DOG GLOMERULI. R. W. Osgood,* M. Hanley, H. J. Reineck, C. B. Wilson, M. Venkatachalam and J. H. Stein, U. of Tx. Hlth. Sci. Ctr., San Antonio, Tx. and Scripps Institute, LaJolla, Ca.

In the past decade, a great deal of information has been obtained concerning glomerular dynamics. Yet, the data have been obtained totally in superficial nephrons. Further, it has not been possible to determine whether a given change in glomerular dynamics was due to a direct effect or secondary to a systemic hemodynamic alteration. Therefore, it seemed advantageous to develop an in-vitro technique to measure glomerular dynamics. Utilizing a method similar to that designed for isolated tubular perfusion, the afferent arteriole is catheterized and perfused with an artificial solution containing 4 gm of albumin and tracer amounts of ^{131}I Albumin. The efferent arteriole is also cannulated for total collection of post-glomerular flow, and glomerular capillary pressure is measured with a pressure measuring pipette threaded through the afferent arteriole into the glomerulus. In five studies, the glomerulus was perfused at an average rate of 195 nl/min and the following results were obtained: glomerular filtration rate (30±8 SEM nl/min), filtration fraction (0.18±.04), glomerular capillary pressure (32±2 mmHg), and ultrafiltration coefficient (1.9±0.3 nl/mmHg/min). Further, the isolated glomeruli were normal histologically as judged by both light and electron microscopy.

Lastly, we have performed studies to determine whether specific uptake of anti-dog glomerular basement membrane antibody (AGBM) or immune complexes could be detected in a single glomerulus. There was no uptake of the particular complex under study while AGBM deposition was readily detectable.

Thus, it seems that isolated glomerular perfusion can be utilized to study various aspects of glomerular dynamics and the mechanisms of deposition of immunologic substances.

PROSTAGLANDINS PARTICIPATE IN THE CONTROL OF RENAL BLOOD FLOW DURING ACUTE HEART FAILURE. J.A. Oliver, R.R. Sciacca,* J. Pinto,* and P.J. Cannon. Columbia University, New York, NY.

To determine whether renal prostaglandins (PG) participate in the regulation of renal blood flow (RBF) during acute heart failure, cardiac venous return was decreased in 17 anesthetized dogs by inflating a balloon in the thoracic inferior vena cava; this decreased cardiac output (CO) from 3.69 ± 0.90 L/min (mean ± SEM) to 2.15 ± 0.19 L/min ($p<0.01$) and mean arterial pressure (MAP) from 132 ± 4 to 111 ± 5 mmHg ($p<0.01$) and increased total peripheral vascular resistance (TPVR) from 37.6 ± 2.5 to 57.9 ± 4.8 RU ($p<0.01$). In contrast, insignificant changes in (RBF) from 224 ± 16 to 203 ± 19 ml/min and renal vascular resistance (RVR) from 0.66 ± 0.06 to 0.61 ± 0.05 were observed. Plasma renin activity and plasma norepinephrine concentration increased in both arterial and renal venous bloods; PGE_2 in renal venous blood increased from 34 ± 6 to 129 ± 24 pg/ml ($p<0.01$). The subsequent administration of indomethacin or meclofenamate had no significant effect on MAP, CO and TPVR but reduced RBF to 156 ± 21 ml/min ($p<0.01$) and increased RVR to 1.05 ± 0.21 ru ($p<0.01$); simultaneously, PGE_2 in renal venous blood fell to 19 ± 3 pg/ml ($p<0.1$). In 5 dogs without obstruction of the vena cava, indomethacin had no effect upon RBF or RVR. The results indicate that acute reduction of CO enhances renin secretion and renal adrenergic activity as well as renal PG synthesis without significantly changing RBF or RVR. Inhibition of PG synthesis during acute heart failure increased RVR and reduced RBF. The data suggest that in the kidney PG counteract the vasoconstrictor mechanisms activated during acute heart failure.

STEREOSPECIFIC INHIBITION OF THE TUBULO-GLOMERULAR FEEDBACK (TGF) AND CHLORIDE TRANSPORT IN THE LOOP OF HENLE BY THE NEW DIURETIC OZOLINONE. H. Osswald,* and H. Hermes,* (intr. by W.S. Spielman). Dept. of Pharmacology, RWTH 5100 Aachen, Fed. Rep. of Germany.

Ozolinone is a new diuretic with potency similar to furosemide. The optically active isomere of ozolinone (l-ozo) induces diuresis, the dextrorotatory form (d-ozo) is inactive. Taking advantage of this fact we asked ourselves whether inhibition of chloride transport in the loop of Henle and inhibition of TGF as seen with other loop diuretics are causally related or just a coincidence due to an unknown action of loop diuretics on the juxtaglomerular apparatus. In Sprague-Dawley rats prepared for micropuncture the nephron was orthograde perfused from end proximal by means of two microperfusion pumps. Stop flow pressure (SFP) was monitored in the first accessible loop of the proximal tubule. A wax block was used to separate the two tubular segments. SFP decreased following elevation of end proximal perfusion rate from 0 to 50 nl/min from 36±1 to 27±1 mmHg (n=16; ±SE). d-Ozo did not affect this normal response. However, l-ozo infused into the same nephron abolished TGF completely. Chloride transport in the loop of Henle was 2.32±.1 nmol/min during d-ozo perfusion at 40 nl/min and only 1.08±.1 nmol/min during l-ozo perfusion. Our data support the concept that chloride transport in the loop of Henle and TGF are causally related.

EFFECT OF KALLIKREIN(KAL) AND PROSTAGLANDIN (PG) INHIBITION ON KININ(KI) EXCRETION AND RENAL RESPONSE TO FUROSEMIDE. A. Overlack*, K.O. Stumpe*, M. Higuchi*, M. Mueller* and R. Kolloch, Med.Univ.Poliklinik, Bonn, FRG.

Urinary excretions of KAL, KI, sodium and water, glomerular filtration rate(GFR) and renal blood flow(RBF) were studied in 12 normotensive subjects before and after furosemide(F;40mg i.v.) alone or in combination either with KAL inhibition by aprotinin(A;$2x10^6$KIU) or inhibition of PG synthesis by indomethacin(INDO) or both.

F increased KAL and KI ($p<0.01$). KI was correlated to KAL ($r=0.6;p<0.001$). A inhibited KAL activity almost completely and lowered KI before (30 ± 4 vs. 21 ± 4 ng/min; $p<0.05$) but not after F. INDO did not change KAL or KI, whereas A and INDO in combination lowered KI before and after F ($p<0.01$). The F induced rise in sodium and water excretion was enhanced by A, whereas INDO decreased this response to F ($p<0.01$). In combination with A this effect of INDO was abolished. GFR and RBF were stimulated by F ($p<0.01$) but not influenced by A or INDO.

KAL and KI are stimulated by acute increases of diuresis and natriuresis. Renal kinin formation may be mainly determined by KAL activity as indicated by the correlation between KAL and KI. However, the failure of KAL inhibition to decrease KI substantially suggests that in addition to KAL other mechanisms are involved in kinin liberation. Kinins may modify the effect of PG on renal function.

COMPARISON OF RENAL RESPONSES TO ISOTONIC SALINE INFUSIONS INTO PORTAL AND JUGULAR VEIN IN SODIUM-LOADED CONSCIOUS RATS. G.O. Perez and A.J. Valdivieso.* V.A. Medical Center and Dept. of Medicine, University of Miami School of Medicine, Miami, Florida.

The role of the liver in the control of sodium excretion remains undefined. We evaluated the effects on renal sodium handling of portal versus jugular vein infusions of isotonic saline (2% body weight; 0.2 ml/min) for 2 hr in conscious, undisturbed Sprague-Dawley rats receiving either a low salt diet or regular chow plus 0.9% saline for one week. Chronic venous catheter implantation was performed 5-10 days prior to study. There were no differences in renal sodium handling between portal and jugular infusions in animals given a sodium-restricted diet. In sodium-loaded rats, both absolute ($U_{Na}V$) and fractional (FE_{Na}) sodium excretion increased significantly and the values in animals receiving portal infusions exceeded those of systemically infused rats at 30 and 60 min post infusion. Peak $U_{Na}V$ in the sodium-loaded animals was significantly higher after portal than after jugular infusions (Portal: 1.1 ± 0.2; Jugular: 0.5 ± 0.1 μEq/min; $P<0.025$). Sodium-loaded animals infused in the portal vein excreted 5 ± 1.0% of the administered dose in one hr while the jugular group excreted only 1.5 ± 0.4% ($P<0.025$). There were no differences in hematocrit, serum sodium, potassium, inulin clearance and filtered load of sodium between portal and systemically infused animals on either diet. The results provide evidence for the participation of the liver in the control of sodium excretion and suggest that the enhanced $U_{Na}V$ after portal administration of saline results from inhibition of renal tubular sodium reabsorption.

EVIDENCE OF COMPETITION FOR ACTIVE UPTAKE BY GENTAMICIN (G) AND NETILMICIN (Ne) IN HUMAN AND RAT RENAL CORTEX. Richard A. Parker, W. Clayton Elliott, George A. Porter, and William M. Bennett. Univ. of Oregon Hlth. Sci. Ctr, Div. of Nephrol., Portland, Oregon.

To better characterize transport of aminoglycosides, we studied cortical slices from four kidneys preserved for renal transplantation but not utilized. Slices were incubated in the presence of 7.6×10^{-3}M H^3 G and concentrations of Ne ranging from 10^{-4} - 10^{-6}M in modified Cross and Taggart media for 90 minutes at 25°C under 100% O_2. Uptake was expressed as slice to media ratio (SM). The active component of uptake (SMA) was calculated by subtracting uptake observed in slices treated with the metabolic inhibitor, iodoacetate. Fresh cortical slices from F344 rats are shown for comparison.

	HUMAN (n=4)		RAT (n=8)	
Ne (M)	G SM	G SMA	G SM	G SMA
0	4.96±.75	1.36±.31	6.06±.73	2.97±.73
10^{-6}	4.05±.93	.70±.54	4.42±.76	1.68±.76
10^{-5}	3.54±.80	.46±.46	3.48±.31	1.14±.31
10^{-4}	1.85±.25	.22±.12	2.04±.49	.18±.46

Values represent means ± SD

These results suggest that G and Ne compete for a saturable, active transport site in both rat and human renal cortex.

ON THE MECHANISM OF THE CONCENTRATING DEFECT (CD) IN POTASSIUM (K) DEPLETION: THE ROLE OF PAPILLARY PLASMA FLOW (PPF). L.N. Peterson,* (intr. by Martin Hutt). Depts. Physiol. & Med., Univ. Colo. Hlth. Sci. Ctr., Denver, CO.

Decreased PPF, as assessed by radioactive albumin accumulation, has been implicated as a contributing factor in the development of the CD associated with K depletion (Whinnery et al, AJP 237: F226, 1979). Because of the effect of K depletion to stimulate thirst and because increased water intake may in itself impair renal concentration, the role of PPF in this CD was further examined in the present study in rats with controlled fluid intake. In age and weight matched controls (C) and K depleted rats receiving the same fluid intake, overnight fluid deprivation was associated with a diminished urinary osmolality (Uosm) after 24 days of low K intake as compared to C rats (2949 vs 1417 mOsm/kg, $p<.001$). As previously reported PPF was also diminished in the K depleted as compared to the C rats (8.4 vs 19.6 ml/min/100 g papillary weight, $p<.001$). Similar studies were then performed after 14 days on a K depleted diet and again a CD was found (1757 vs 2949 mOsm/kg, $p<.05$). However, this CD was not associated with a decrease in PPF (18.8 vs 19.6 ml/min/100 g papillary weight). The results of this study therefore indicate that a diminished PPF may contribute to the concentrating defect observed after 24 days of K depletion. However, the CD after 14 days of a K depleted diet can be dissociated from a diminution in PPF, thus implicating as yet other undefined factor(s).

EFFECT OF CATECHOLAMINES ON THE POTENTIAL DIFFERENCE AND CHLORIDE EFFLUX IN THE MOUSE THICK ASCENDING LIMB OF HENLE'S LOOP. R.E. Polhemus* and D.A. Hall, Stanford University and the Veterans Administration Medical Center, Palo Alto, California.

To separate the direct tubular from the indirect vascular effects of catecholamines on nephron transport function, mouse medullary thick ascending limbs were isolated, perfused, and exposed to catecholamines in vitro. The perfusate and bath were a modified Ringers solution. The bath contained 5% calf serum. Potential differences and isotopically determined chloride effluxes were measured.

The addition of 10^{-6}M isoproterenol (ISO) to the bath increased the PD from 4.1 ± 1.4 mv to 8.3 ± 1.7 mv (n=5, p<.001). Removal of ISO returned the PD to base line. 10^{-6}M ISO also increased the chloride efflux from 47.3 ± 12.0 peq/cm/sec to 77.3 ± 14.6 peq/cm/sec (n=5, p<.05). The addition of 10^{-6}M norepinephrine (NE) to the bath also increased the PD (4.8 ± .7 mv to 7.8 ± 1.4 mv, n=6, p<.05). Submaximal PD responses were observed in some tubules with NE concentrations as low as 10^{-9}M. Propranolol 10^{-6}M could block completely the effects of NE on PD, while propanolol 10^{-6}M alone had no effect on the base line PD.

We conclude that β adrenergic stimulation increases the lumen positive PD and chloride efflux in the mouse medullary thick ascending limb. This suggests that β adrenergic agents may directly stimulate chloride transport in this segment of the nephron.

GLUCAGON, A POSSIBLE HORMONAL REGULATOR OF POTASSIUM EXCRETION IN SHEEP. L. Rabinowitz, R. L. Sarason*, and H. Yamauchi. School of Medicine, University of California, Davis, California.

Administration of exogenous glucagon increases sodium and potassium excretion in men and dogs. In sheep after ingestion of a typical, K-rich meal both plasma glucagon and U_KV increase. 3 mature ewes were studied to determine the effects of glucagon on Na and K excretion in sheep. Glucagon, 1 mg bolus iv to 24-hr fasted sheep, produced within 30 min a decrease in $U_{Na}V$ (-85 uEq/min), an increase in Pglucose (+63mg%), and an initial decrease in U_KV (-102 uEq/min) that was followed within 30 min by a large increase in U_KV (+120 uEq/min), all changes relative to control values in the same sheep without treatment. Proprionate, a major product of rumen fermentation, stimulates both glucagon and insulin secretion in sheep. Proprionate, 15 millimoles bolus iv given to fasted sheep provoked within 30 min increases in Pglucose (+12mg%) and in U_KV (+65 uEq/min), and a decrease in $U_{Na}V$ (-60 uEq/min). Increases in U_KV were directly proportional to the hyperglycemia produced by glucagon and proprionate. All increases in U_KV were paralleled by decreases in plasma K (-.45 mEq/l with glucagon and -.33 mEq/l with proprionate). These results are compatible with the following physiologic reactions. Glucagon, both exogenous and proprionate-stimulated, promoted K excretion and hyperglycemia. Proprionate and hyperglycemia stimulated insulin secretion. Insulin promoted both cellular K influx over efflux and depressed Na excretion, an action of insulin previously demonstrated in men and dogs.

INFLUENCE OF VOLUME EXPANSION ON Mg INFLUX INTO THE SUPERFICIAL PROXIMAL TUBULE. Gary A. Quamme, Dept. of Medicine, Acute Care Unit, University of British Columbia, Vancouver, British Columbia, Canada.

The proximal tubule is poorly permeable to Mg relative to sodium or calcium. To determine the effect of volume expansion on luminal Mg entry, superficial proximal tubules were perfused in vivo with magnesium-free Ringer's solutions. Tubules were perfused at 25 nl/min and fluid collected downstream at an early (EP) and a late (LP) site of the same nephron. In hydropenic rats, absolute Mg concentration was 0.03 ± 0.02 mM/l at EP and 0.065 + 0.02 mM/l at LP located 0.15 ± 0.04 mm and 2.13 ± 0.21 mm respectively from the perfusion site (n = 17). Volume expansion to 5% b.w. with Ringer's resulted in an increase in fractional urinary excretion of Na 0.04% to 1.2% and Mg 16% to 36%. Luminal Mg rose to 0.07 ± 0.02 mM/l at EP and 0.15 + 0.04 mM/l at LP located 0.30 ± 0.13 and 2.58 ± 0.38 mm from the perfusion site (n = 14). Volume expansion resulted in a decline of net water reabsorption from 2.98 to 2.51 nl/min/mm and Mg influx was 0.57 and 1.07 pM/min/mm at LP. Correlation of net water reabsorption with Mg influx reveals that water reabsorption proceeded faster than Mg influx between EP and LP suggesting that the equilibrium values for Mg are less than those observed at LP in both hydropenia and volume expansion. Further, fractional Mg reabsorption proceeds at a slower rate than net water reabsorption in both conditions. We conclude that influx of Mg does occur in the proximal tubule and the magnitude is dependent on the extracellular volume status of the animal.

LOCALIZATION OF THE Na^+-SUGAR COTRANSPORT SYSTEM IN A KIDNEY EPITHELIAL CELL LINE. Carlos A. Rabito* Dept. of Medicine, Harvard Medical School and The Massachusetts General Hospital, Boston.

Studies on the localization of the Na^+ dependent sugar transport in monolayers of LLC PK_1 cells show that the uptake of αmethyl-D-glycoside (αMGP), occurs mainly from the apical side of the monolayer. In addition (^3H) phlorizin binding to monolayers of LLC PK_1 cells were also measured. These studies demonstrate the presence of two distinct classes of receptor sites. The class comprising high affinity binding sites had a dissociation constant (K_D) of 1.2 μM and a concentration of high affinity receptors of .30 μmole of binding sites per g DNA. The other class involving low affinity sites had a K_D of 240 μM with the number of binding sites equal to 12 μmole of DNA^{-1}. Phlorizin binding at high affinity binding sites is a Na^+ dependent process. Na^+ increases the affinity of phlorizin to the high affinity receptors without modifying the number of binding sites. The Na^+ dependence and the matching of K_D for high affinity binding sites with the Ki (1.1 μM) of phlorizin for the inhibition of αMGP strongly suggest that the high affinity phlorizin binding site is, or is part of the αMGP transport system. Binding studies from either side of the monolayer also show that the binding of phlorizin at the Na^+ dependent high affinity binding sites occurs mainly from the apical rather than the basolateral side. The specific location of the Na^+ dependent sugar transport system in the apical membranes of LLC PK_1 cells is, therefore, another expression of the functional polarization of epithelial cells that is retained under tissue culture condition.

● REVERSIBLE FIXATION OF VASOPRESSIN-INDUCED MEMBRANE EVENTS BY IMIDOESTERS. J. Rapoport† W. Kachadorian, J. Muller† N. Franki† & R.M. Hays. Albert Einstein Coll. Med. & Renal Service, USPHS Hosp., NY, NY.

Vasopressin (VP) induces fusion of elongated cytoplasmic vesicles with the luminal membrane of the toad bladder, and the delivery of particles, presumed to conduct water, from vesicular membrane to luminal membrane. Upon hormone withdrawal, aggregates disappear from the luminal membrane, and water flow (ΔW) falls rapidly to baseline. We used the imidoester dithiobispropionimidate (DTBP) which cross-links membrane proteins, to reversibly arrest membrane reorganization following VP withdrawal. Thus, the relationship between aggregates, membrane, and vesicles can be seen at any point in time.

Paired toad urinary bladders were exposed to VP, then one bladder was exposed to 2mg/ml DTBP in the luminal medium. VP was withdrawn, and ΔW, which dropped rapidly to baseline in the control bladder, persisted at 60-70% of maximum in the cross-linked bladder, slowly returning toward baseline. Persistence of ΔW was associated with persistence of membrane aggregates, shown by freeze-fracture electron microscopy (272 ± 44 agg/235μ^2) while aggregates in control bladders virtually disappeared (17 ± 9 agg/235μ^2, $P<0.01$). Following cleavage of the central S-S bond of DTBP by β-mercaptoethanol, ΔW fell rapidly to baseline. While DTBP maintained aggregates in the VP-free membrane at approximately 60% of maximum, it did not maintain vesicle fusion events as effectively (30% of maximum). This suggests that the presence of vesicles fused to the luminal membrane may not be necessary for the disappearance of aggregates, but that a mechanism other than aggregate recapture by vesicles may be involved.

● BICARBONATE REABSORPTION BY THE RAT PAPILLARY COLLECTING DUCT: EFFECT OF ACETAZOLAMIDE. R. M. A. Richardson* and R. T. Kunau, Univ. of Tx. Hlth. Sci. Ctr., San Antonio, Texas.

While the collecting duct (CD) is able to establish steep hydrogen ion gradients, its capacity to reabsorb bicarbonate (HCO_3) has been assumed to be low. The present study was designed to examine the capacity of the CD to reabsorb HCO_3 as delivered load is increased by HCO_3 infusion and the effect of the carbonic anhydrase inhibitor, acetazolamide (ACZ), on HCO_3 reabsorption by this nephron segment. To induce bicarbonaturia, six control Munich-Wistar rats (C), 140-200g, were given .5 ml of 1.0M $NaHCO_3$ and 5-10% body weight of an isotonic infusion containing 75 mM $NaHCO_3$. CD samples from the papillary base and tip, 2.0 mm apart, were obtained by micropuncture and analyzed for ^{3}H inulin and total CO_2 (tCO_2) by microcalorimetry. Three other rats were given ACZ 20 mg/Kg IV bolus and 20 mg/Kg/hr in isotonic $NaHCO_3$ at 40 μl/min. In C rats fractional tCO_2 delivery to the papillary base ($FDtCO_2$) ranged from 1.6 to 27.5%. Reabsorption of tCO_2 along the papillary CD increased linearly with delivery, ranging from .6 to 16.8% of filtered load. These results indicate that the papillary CD has a significant capacity to reabsorb tCO_2. In order to facilitate comparison of C and ACZ rats, CD tCO_2 reabsorption was analyzed at comparable absolute delivery rates of tCO_2. Absolute delivery was calculated from the contralateral kidney GFR, the plasma tCO_2 and FD tCO_2 to the papillary base. In the range of absolute delivery rates of tCO_2 to the papillary base of 2 to 10 μEq/min, C rats reabsorbed 42 ± 5% of this delivered load, whereas ACZ rats reabsorbed only 7 ± 4% ($p<.001$).

Conclusions: The papillary CD of the rat has a capacity to reabsorb HCO_3 which is greater than previously recognized. CD HCO_3 reabsorption is inhibited by acetazolamide.

● EFFECT OF MEDULLARY TONICITY ON URINARY SODIUM EXCRETION. H. J. Reineck and R. Parma*. U. of Tx. Hlth. Sci. Ctr., Dept. of Med., San Antonio, Tx.

In a previous study from this laboratory we suggested that a reduction in medullary tonicity decreases ascending loop of Henle reabsorption and is in part responsible for the magnitude of the natriuresis accompanying 10% body weight Ringer loading. According to this postulate, one would expect that the medullary washout associated with water diuresis would result in a natriuresis, a phenomenon which does not occur. It is possible, however, that increased distal delivery out of the proximal tubule is necessary to demonstrate an effect of medullary tonicity on urinary sodium excretion. Micropuncture studies were designed to test this possibility. In the first series of studies four groups of animals were examined: hydropenia (H), clonidine-induced water diuresis (WD), 2% body weight Ringer loading (R), and R plus WD (RWD). Vasa recta osmolalities were significantly reduced in WD and RWD (390 and 342 mOsm/Kg H_2O, respectively) compared to H (1004) and R (720). Fractional delivery of sodium out of the proximal tubule of superficial (SN) and juxtamedullary nephrons (JMN) was similar in H and WD. Ringer loading increased these values equally in R and RWD. Yet, the fractional excretion of sodium (FE_{Na}) was significantly increased only in RWD (2.2%) compared to 0.3% in H and 0.1% in WD and R. To exclude a direct effect of clonidine or ADH on distal sodium transport a second group of studies were performed in which medullary tonicity was reduced by 1 h. of papillary exposure. Uosm from the exposed kidney (E) and unexposed kidney (UE) averaged 485 and 1160 respectively. Following 2% Ringer loading FE_{Na} was 2.7% from E and only 0.7% from UE. These studies indicate that when delivery out of the proximal tubule of SN and JMN is adequately increased, a decrease in medullary tonicity results in diminished distal reabsorption and increased urinary sodium excretion.

EFFECT OF SALT DEPLETION AND HEMORRHAGE ON ULTRAFILTRATION COEFFICIENT (K_f) IN ISOLATED GLOMERULI. S.M. Ridge*, R.V. Patak and V.J. Savin*. University of Kansas Medical Center, Kansas City, KS.

In vivo studies have shown decreased K_f after salt depletion. We investigated the effects of salt depletion and hemorrhage on K_f using isolated glomeruli (Kid Int 12:572, 1977). The following conditions were studied: control, low Na^+ diet x 3-7 weeks, low Na^+ diet + 30 mg/kg furosemide x 3 days, low Na^+ diet + 240 mg/kg furosemide x 1, low Na^+ diet + 3% body weight hemorrhage.

Group	K_f (nl/min·mmHg)	S_{Cr} (mg/dl)
Control (10)	3.96 ± 0.24	0.62 ± 0.04
Low Na (6)	3.29 ± 0.20	0.70 ± 0.07
Low furosemide (6)	3.10 ± 0.21	0.72 ± 0.04
High furosemide (4)	2.61 ± 0.28	2.63 ± 0.55
Hemorrhage (4)	2.33 ± 0.25	2.33 ± 1.07

The change in K_f was significant at $p < 0.05$ in low Na^+ and low furosemide and at $p < 0.005$ in high furosemide and hemorrhage groups. Serum creatinine increased significantly in high furosemide and hemorrhage groups. Other significant changes included: decreased body weight in high furosemide; decreased Hct in hemorrhage and increased Hct in high furosemide; increased serum protein in high furosemide. We conclude that severe volume depletion and hemorrhage are associated with a marked decreased in K_f. Restriction of dietary Na^+ alone or with moderate furosemide administration produces a smaller decrement in K_f. These studies suggest that the renal response to volume depletion may be mediated not only by hemodynamic and tubular mechanisms but also by alterations in K_f.

DENERVATION DIURESIS AND NATRIURESIS IN CONSCIOUS RATS. Paula R. Rogenes* and Carl W. Gottschalk. U.N.C., Dept. of Physiol., Chapel Hill, N.C.

Unilateral renal denervation (URD) results in diuresis and natriuresis from the denervated kidney in anesthetized rats and dogs, but these effects have not been seen in conscious dogs. We studied individual kidney function in conscious rats 7 to 9 days after URD (n=11) or sham denervation (n=5). On the day of study, rats were anesthetized with ether to permit vascular and ureteral cannulation, placed in a restraining chamber, and allowed to recover for at least 3 hr. Each animal was studied under three conditions: conscious and euvolemic (cEu); conscious and volume expanded to 3% body wt with isotonic saline (cVE); and under pentobarbital anesthesia and VE (aVE).

No differences in renal function were observed between the two kidneys of sham denervated animals. C_{In} and C_{PAH} were greater from the denervated kidney in the URD rats during cEu but not after VE.

		cEu	cVE	aVE
$\dot{V}$, µl/min	I	9.8*	34.2*	19.7**
	D	16.4*	43.7*	50.3**
$U_{Na}\dot{V}$, µEq/min	I	0.9*	4.2**	2.4**
	D	1.8*	6.5**	8.2**

I=innervated kidney; D=denervated kidney
* $p<0.05$, I vs. D; ** $p<0.01$, I vs. D

Denervation diuresis and natriuresis were observed in conscious rats during euvolemia and following VE. These effects were independent of hemodynamic factors in the VE state. Following anesthesia, changes in excretion by each kidney increased the differences between the innervated and denervated sides. These results demonstrate that the effects of chronic URD on renal function occur in conscious as well as in anesthetized rats.

INTRACELLULAR SODIUM ACTIVITY IN AMBYSTOMA RENAL PROXIMAL TUBULE. H. Sackin*, W. Boron* and E.L. Boulpaep (intr. by E. Hendler). Yale Univ., Dept. Physiol., New Haven, CT 06510.

Intracellular Na activities were measured in isolated perfused salamander (Ambystona tigrinum) proximal tubules using both recessed-tip Na-selective glass and liquid ion exchanger microelectrodes. The mean intracellular Na activity was 24.0±2.6mEq/L (n=8 tubules) using Na-selective glass, not significantly different from 23.4±1.3 mEq/L (n=7 tubules) using liquid ion exchanger. With normal bath Na, replacement of luminal Na with tetramethylammonium (TMA) decreases intracellular Na activity from 25.5±5.1mEq/L to 10.7±3.9mEq/L in 3 minutes, decreasing at an initial rate of -.08±.04(mEq/L)/sec (n=3). However with normal luminal Na, replacement of bath Na with TMA, choline or sucrose decreases intracellular Na activity from 21.1±2.5mEq/L to 7.3±.6mEq/L in 1 minute, decreasing at an initial rate of -.54±.15(mEq/L)/sec (n=7). In absence of Na in both lumen and bath, mean intracellular Na activity is 2.53±.7mEq/L (n=6). At this point return of normal Na to the lumen only, increases cell Na at an initial rate of .15±.04(mEq/L)/sec (n=4). In contrast, return of normal Na to the bath only, increases cell Na at an initial rate of .33±.08(mEq/L)/sec (n=6). It is assumed that increases in intracellular Na resulting from return of luminal Na in the absence of bath Na or resulting from return of bath Na in the absence of luminal Na represent a minimum estimate, respectively, of the lumen to cell or the bath to cell passive Na flux. Hence, the minimum estimate of luminal membrane Na permeability is $3.4\pm6\times10^{-6}$cm/sec (n=4), and of basolateral membrane Na permeability is $2.2\pm.5\times10^{-6}$cm/sec (n=6).

EFFECT OF ACUTE METABOLIC ACIDOSIS ON POTASSIUM DELIVERY TO THE END-DESCENDING LIMB OF THE JUXTAMEDULLARY NEPHRON. Denis Roy,* Kristina L. Blouch* and Rex L. Jamison. Div. of Nephrology, Stanford University Medical Center, Stanford, California.

To determine the effect of acute metabolic acidosis on fractional delivery of K (FD-K) at the end-descending limb (DL) of the juxtamedullary (JM) nephron, we performed micropuncture of the exposed left renal papilla in 7 hydropenic rats made acutely acidotic with HCl (2.5 mEq/kg) (pH=7.24±0.02,SE) and in 7 control rats given vehicle only (pH=7.39± 0.03; P<0.01). Compared to control rats, urine-to-plasma inulin (U/P In) was less (123±9 vs 186±11; P<0.001) and fractional excretion of K (FE-K) (%) was higher (40±2 vs 31±3; P<0.05) in acidosis. GFR, FE-Na, plasma K, urine K and U/P K did not differ significantly. Tubular fluid-to-plasma (TF/P) ratios, FD-Na and FD-K at JM-DL were:

		$\frac{TF}{P}$In	$\frac{TF}{P}$Na	$\frac{TF}{P}$K	FD-Na (%)	FD-K (%)
Control	$\bar{x}$	6.84	1.61	9.09	26	138*
	SE	0.68	0.08	0.94	2.8	14.0
Acidosis	$\bar{x}$	5.84	1.75	7.19	31	125*
	SE	0.37	0.15	0.46	2.0	5.0

(*P<.05, compared to 100%). Differences between the groups, NS. FD-K was a function of FE-K in control ($y = 3.73x + 23.7$; $r = 0.77$; $P<0.05$) but not in acidotic rats ($y = 1.28x + 74$; $r = 0.60$; P= NS). The results are unequivocal evidence of K secretion by the JM-DL or pars recta (and presumably medullary K recycling) in the normal rat which persists in acute acidosis. The failure of FD-K to rise despite increased FE-K in acidosis suggests urine K rather than FE-K is the primary determinant of K recycling.

NEPHRON SITES OF AMMONIA ADDITION IN RATS WITH CHRONIC METABOLIC ACIDOSIS. I.M. Sajo*, M.B. Goldstein, H. Sonnenberg, B.J. Stinebaugh, D.R. Wilson and M.L. Halperin. Univ. of Toronto, Toronto, Canada and Baylor College of Medicine, Houston, Texas, USA.

The purpose of this study was to examine the sites of ammonia addition to the tubular fluid along the nephron in 5 rats with chronic metabolic acidosis. Samples of tubular fluid were obtained from proximal (PCT) and distal tubule (DCT) by micropuncture, and from medullary collecting duct (MCD) by microcatheterization. Ammonia was assayed by an enzymatic and ion exchange chromatography method and the effect of H_2O reabsorption on intratubular ammonium concentration was assessed by measuring $(TF/P)_{inulin}$.

	$TF_{NH_4^+}$ mM	$(TF/P)_{inulin}$	$NH_4^+/(TF/P)_{inulin}$
PCT	3.2±0.1	2.4± 0.1	1.45±0.13
DCT	4.0±0.7	7.8± 0.7	0.56±0.11
MCD	40 ±3	31 ± 4	1.44±0.07
Urine	238 ±2	157 ±40	1.76±0.17

Conclusions: 1) Water is abstracted along the nephron. 2) Virtually all (80%) of the excreted NH_4^+ was present in the PCT but only 30% was present in the DCT. 3) NH_4^+ reappears in the MCD fluid, 2/3 via the cortical CD and 1/3 via the MCD. These data indicate that medullary structures play an important role in NH_4^+ excretion.

CHARACTERISTICS OF RENAL BRUSH BORDER CARBONIC ANHYDRASE (CA). RW Schmidt & F Crowley. Univ of Calif & VA Med Ctr, San Francisco, CA.

Microvesicles of dog renal brush border membranes (BBM) were prepared by $CaCl_2$ aggregation and sucrose gradient centrifugation. Electronmicrography demonstrated a uniform vesicle preparation which was enriched 13.7X in alkaline phosphatase (alk p'tase). Titrimetric assay of the CO_2 hydration reaction demonstrated CA activity in BBM accounting for 3% of total renal CA. Inhibition of CA by acetazolamide (Atz), benzolamide (Benz) and chloride (Cl) was measured. Comparisons to cytosol, RBC and Bovine CA were made.

	BBM	Cytosol	RBC	Bovine	Units
K_m CO_2	9.4	7.8	13.9	7.6	10^{-3}M
K_i Atz	4.7	3.2	3.6	2.7	10^{-9}M
K_i Benz	0.4	0.4	0.6	0.4	10^{-9}M
K_i Cl	228	186	-	180	10^{-3}M

Protein was solubilized from BBM to different degrees by treatment with Triton X-100, SDS, alkaline pH or sonication in order to assess the binding strength of CA to BBM as compared to alk p'tase, an integral membrane protein. Alkaline pH and sonication removed BBM protein to variable degrees, but not CA or alk p'tase. Triton and SDS solubilized these enzymes, but the extent of removal was much less than for other proteins. Under all conditions CA solubilization paralleled alk p'tase.

We conclude that BBM contains CA which is functionally similar to renal cytosol CA, RBC CA, and bovine CA. The CA located on the BBM is bound to the membrane structure, but may be removed intact by Triton X-100 or SDS treatment.

FUNCTIONAL ANATOMY OF THE MAMMALIAN RENAL PAPILLA. Bodil Schmidt-Nielsen and Bruce Graves. Mt. Desert Island Biological Laboratory, Salsbury Cove, ME.

It has been shown that peristaltic contractions of the renal pelvic wall in rodents exert a milking action upon the papillary collecting ducts (PCD) (Schmidt-Nielsen et al., Kid. Internat., in press). The PCD are squeezed empty during the peristaltic contraction and remain empty for a period of time following the contraction. At low urine flow rate, PCD are empty up to 95% of the time. This opening and closing of the PCD is of considerable functional interest in itself, but in addition it may change the flow through the vasa recta and loops of Henle. To examine the state of the PCD during various functional conditions, papillae of Syrian hamsters were fixed (with osmotically adjusted glutaraldehyde fixative) a) in situ through the pelvic wall in diuresis and in antidiuresis, and b) in situ in diuresis and antidiuresis after removal of the pelvic wall. One µm sections were made perpendicular to the long axis of the papilla at distances from the tip of 0.5, 1,2,3 and 4 mm. In antidiuretic hamsters with renal pelvis intact, PCD lumina were closed or almost closed, the PCD circumference was greatly reduced, and the area between PCD, which includes vasa recta and loops of Henle was greatly increased. In mannitol diuretic hamsters fixed with the renal pelvis intact, the PCD were open and were not very different from those of mannitol diuretic hamstes with pelvic wall removed, or from antidiuretic hamsters with pelvic wall removed. It is concluded that a major shift takes place in relative size of loops of Henle, vasa recta and PCD when the PCD are empty.

CONTRIBUTION OF TUBULO-GLOMERULAR FEEDBACK (TGF), ANGIOTENSIN II (AII), AND PROSTAGLANDINS (PG) TO AUTOREGULATION OF NEPHRON FILTRATION RATE (SNGFR). Jürgen Schnermann*, Josephine Briggs, and Peter C. Weber*(intr.by D.Z.Levine). Depts. of Physiology and Internal Medicine, Univ. of Munich, W-Germany

Experiments were done in euvolemic, plasma replaced rats to examine the contribution of TGF,PG, and AII to regulation of SNGFR during reduction of renal perfusion pressure by supra-renal aortic constriction. SNGFR was determined at 3 levels of arterial pressure (AP) with all mechanisms intact (control distal collections,CDC), and after elimination of TGF (control prox coll,CPC), PG synthesis (indomethacin dist coll,IDC), and AII (saralasin dist coll,SDC). Main results are summarized (mean±SE):

	SNGFR (nl/min)			ΔSNGFR/ΔAP	
AP (mm Hg)	115	95	77	115-95	95-77
CDC	31.8±1.3	31.7±1.6	29.3±1.5	.006	.13
CPC	40.8±1.7	36.4±2.2	31.0±1.6	.263	.26
SDC	32.0±1.0	30.7±1.6	26.0±1.2	.011	.26
IDC	38.6±1.4	34.0±1.7	25.3±1.3	.15	.47

The increase in plasma renin concentration in control (7.5 to 61 ng AI/ml/hr,AP from 115 to 77) was blunted by indomethacin (3.5 to 15). Conclusions: a)in euvolemic rats autoregulation of SNGFR is operative to a pressure of about 80 mm Hg; b)TGF contributes to autoregulation in both the higher (115 -95) and lower (95-77) pressure ranges; c)an effect of AII on autoregulation is demonstrable only in the lower range; d)renal PG are required for autoregulation and their importance is most pronounced in the lower range; this effect of PG may be related to their own vasodilatory action, to their involvement in TGF, or to their role in the control of renin release.

Na^+-H^+ EXCHANGE IN THE RABBIT RENAL PROXIMAL TUBULE. George J. Schwartz. Department of Pediatrics, Albert Einstein College of Medicine, Bronx, New York 10461.

Removal of Na^+ or addition of ouabain inhibits HCO_3^- and Na^+ absorption in the rabbit proximal tubule, a finding suggestive of direct Na^+-H^+ coupling. However, inhibition of Na^+ transport might decrease H^+ secretion indirectly by reducing energy metabolism. Efflux of H^+ which, as shown in brush border vesicles, depends on the direction of the Na^+ gradient, should be a function of proximal cell Na^+, independent of cellular metabolism. If cell Na^+ is increased by ouabain H^+ efflux should increase. When cell Na^+ is reduced by Na^+ removal, less H^+ should leave the lumen for a given pH difference. Superficial early proximal convoluted tubules were dissected from rabbit kidney and perfused at a rate of 10-80 nl/min mm in vitro with CO_2- and HCO_3^--free solutions (pH 6.45). The bath resembled the perfusate except that the pH was 7.4 and it contained 6 gm/dl of albumin. The pH of the fluid was measured as it emerged from the tubule with a glass microelectrode. H^+ efflux was calculated from the difference in pH between perfused and collected fluid, the flow rate, and the buffer capacity of the perfusate. When 150 mM Na^+ was present in perfusate and bath, H^+ efflux was 5.3±.4 pmol/cm s (n=20) and increased by 39±16% when ouabain $5x10^{-3}$M was added to the bath (n=6, $p < .05$). Replacement of Na^+ by choline (n=9) or lithium (n=5) caused a 44±7% decrease in H^+ efflux ($p < .02$). Similarly, addition of amiloride 10^{-4}M to a 10mM Na^+ medium caused a 34±6% reduction in H^+ efflux (n=5, $p < .02$).

The results show that H^+ transport in the proximal tubule is mediated, at least in part, by a reversible Na^+-H^+ exchanger driven by a difference between H^+ and Na^+ gradients.

MECHANISM OF CL TRANSPORT IN NECTURUS RENAL MICROVILLUS MEMBRANE VESICLES (MMV). Julian Seifter*, James L. Kinsella*, and Peter S. Aronson. Yale Sch. Med., Depts of Med. & Physiol., New Haven, CT.

Based on measurements of intracellular Cl^-, Spring and Kimura (JMB. 38: 233, 1978) concluded that Cl^- transport across the luminal membrane of the Necturus proximal tubular cell is a Na^+-coupled uphill process. We have attempted to characterize Cl^- transport pathways in MMV isolated from Necturus kidneys by a Mg-aggregation method. The initial rate of uptake of $^{36}Cl^-$ (10mM or 50mM) was identical in the presence of 40mM external K^+, Li^+ or Na^+, arguing against the existence of Na^+-Cl^- cotransport. Supporting the presence of an anion exchanger with affinity for Cl^- and HCO_3^- was the finding that, when MMV were preloaded with $^{36}Cl^-$ (30mM), the initial rate of Cl^- efflux into media containing 60mM Cl^- or HCO_3^- was 2-3X greater than into 60mM gluconate. This stimulation of $^{36}Cl^-$ efflux by external Cl^- or HCO_3^- was unaffected by shunting of the membrane potential to 0mV with valinomycin in the presence of $K^+_{in}=K^+_{out}$ (30mM). Moreover, the disulfonic stilbene SITS (2mM) completely abolished the stimulation of $^{36}Cl^-$ efflux by external Cl^-. Finally, the initial rate of 1mM $^{22}Na^+$ uptake was 2X greater in the presence of an initial pH gradient (pH_i=6.0, pH_o=7.5) than under control conditions ($pH_i=pH_o$=7.5) and this stimulation was completely abolished by 0.5mM amiloride, a known inhibitor of Na^+-H^+ exchange in rabbit renal MMV. These studies suggest that Na^+-coupled uphill Cl^- transport across the luminal membrane arises not from direct Na^+-Cl^- cotransport but from the parallel operation of a SITS-sensitive anion exchanger with affinity for Cl^- and HCO_3^- and of an amiloride-sensitive Na^+-H^+ exchanger.

EFFECTS OF WATER DIURESIS AND ANTIDIURESIS INDUCED BY DEHYDRATION OR DDAVP ON URINARY PROSTAGLANDIN E_2 EXCRETION IN MAN. A.L. Siu and J.N. Forrest, Jr., Yale Univ. Sch. Med., New Haven, CT.

Although PGE_2 has been proposed as a regulator of the cellular action of antidiuretic hormone (ADH), data on the effects of ADH on urinary PGE_2 excretion in animals are conflicting. Therefore, we studied the effects of physiologic antidiuresis and water diuresis (WD) in man by serial measurements in 7 human subjects beginning with overnight dehydration (OD) followed by sustained water diuresis (2ml/kg BW) followed by return to antidiuresis induced by either 8 hr dehydration (8hD) or exogenous DDAVP (1$0\mu$g). Urine osmolality was 937±179 mOsm/kg following OD, 70±8 during WD, 746 ± 36 after 8hD and 692 ± 62 after DDAVP. Urinary flow rates varied from 0.65± 0.07 ml/min (OD) to 11.3 ± 1.4 (WD). Urine samples were assayed at several dilutions by RIA with a specific PGE_2 antibody (Dray). PGE_2 excretion was 125 ± 25 pg/min after OD, rose to 1053 ± 209 during peak WD, and fell to 170 ± 33 and 117 ± 10 after 8hD or DDAVP. Urine flow rate and PGE_2 excretion correlated linearly during all periods ($r=0.72$, $p < 0.001$, $n=74$). Increased PGE_2 excretion was not due to washout of bladder dead space or changes in GFR since creatinine excretion and clearance were not different between periods. These studies indicate that in conscious man (1) antidiuresis induced by either endogenous or exogenous ADH is not accompanied by increased PGE_2 excretion; (2) during WD, PGE_2 excretion is increased 8 fold above baseline and varies directly with urine flow. The data suggest that in man antidiuresis is not accompanied by increased renal PGE_2 production and that urine flow rates are an important determinant of PGE_2 excretion under physiologic conditions.

URATE TRANSPORT BY THE ISOLATED PERFUSED S_2 SEGMENT OF THE RABBIT. H. O. Senekjian, T. F. Knight, and E. J. Weinman. VA Medical Center and Baylor College of Medicine, Houston, Texas.

Urate transport was studied in isolated, perfused S_2 segments of the superficial proximal tubule of the rabbit. When urate was present in identical concentrations of 290 µM in the perfusing and bathing solutions, there was a net secretory flux of urate of 775.0±152.8 x 10^{-15} M/min/mm. When urate was present in varying concentrations in the bathing solution only, the bath to lumen flux of urate increased as the concentration of urate in the bathing solution was increased from 298 to 595 µM, but tended toward a plateau at higher concentrations. Measurement of the bath to lumen flux of urate when the bathing solution was cooled to 25°C provided an estimate of the passive component of the bath to lumen flux. An apparent passive permeability coefficient (bath to lumen) of 0.94 x 10^{-12} M/min/mm/mM was derived. After correction of the net secretory flux for the contribution of passive permeation, an apparent Km of 238 µM and Vmax of 950 x 10^{-15} M/min/mm for the secretory flux of urate was calculated. The lumen to bath flux of urate was identical when the bathing solution was maintained at 37° or 25°C. The apparent passive permeability coefficient (lumen to bath) was 0.99 x 10^{-12} M/min/mm/mM.

These studies provide evidence for both passive and facilitated mechanisms for urate secretion in the rabbit S_2 segment. The absorptive flux for urate appears to be primarily a passive mechanism. The apparent permeability coefficients are equal in both the absorptive and secretory directions, implying that the passive movement of urate is via a non-rectified pathway.

EFFECTS OF DIURETICS ON PAPILLARY PLASMA FLOW (PPF) IN THE DOG. Samuel Spitalewitz, * Shyan-Yih Chou, Pierre F. Faubert, and Jerome G. Porush. Brookdale Hospital Medical Center, Brooklyn, N.Y.

Previous studies have shown that furosemide (F) and ethacrynic acid (EA) decrease papillary osmolality and increase renal blood flow (RBF) during hydropenia; however, their effects on medullary hemodynamics remain unknown. Following Na balance studies, renal hemodynamics including PPF were measured in 6 hydropenic normal dogs and during euvolemic, steady state diuresis induced by F (3 mg/kg plus 2 mg/kg/h IV) in 6 dogs, EA (3 mg/kg plus 2 mg/kg/h IV) in 6 dogs and chlorothiazide (CTZ-10 mg/kg plus 10 mg/kg/h IV) in 8 dogs. PPF was determined by the albumin accumulation method. Urine flow increased significantly after each diuretic and fractional Na excretion increased from 0.3±0.1 to 16.2±1.5 after F ($p<0.001$), 0.4±0.1 to 25.8±4.0 after EA ($p<0.001$) and 0.3±0.1 to 4.9± 0.8% after CTZ ($p<0.01$). Urine osmolality decreased from 1431±109 to 323±7, 1271±61 to 321±13 and 1381±128 to 676±48 mOsm/kg H_2O after F, EA, and CTZ, respectively ($p<0.001$). Both F and EA increased and CTZ decreased RBF significantly ($p<0.01$). Wet weight papillary water content was similar in all groups. Tissue osmolality was 381± 31 in F and 363±10 in EA dogs, both significantly lower than CTZ dogs, 695±49 mOsm/kg H_2O ($p<0.01$). PPF was 10.8±1.0 in F and 11.3±2.6 ml/min/100g in EA dogs, both significantly lower than normal or CTZ dogs, 26.0±2.1 and 26.7±2.7 ml/min/100g, respectively ($p<0.01$). These studies demonstrate that the reduced papillary osmolality noted with loop diuretics is associated with a decrease in PPF despite an increase in RBF. Furthermore, RBF and PPF were dissociated with all three diuretics.

● EFFECT OF LUMEN pH ON RENAL DISTAL TUBULE POTASSIUM TRANSPORT. Bruce Stanton* and Gerhard Giebisch (intr. by S.Thier) Yale Univ. Sch. Med., New Haven, CT 06510.

The pH of the plasma is one of the factors regulating distal tubule potassium (K) transport. By microperfusion of rat distal tubules *in vivo*, at constant delivery of fluid and buffer, we have shown (Kid. Int. 16: 839, 1979) that distal K secretion is enhanced by metabolic alkalosis and depressed by metabolic acidosis. In the present study we examine the effect of luminal fluid pH on K transport independent of systemic acid-base balance. Distal tubules were microperfused at 20 nl/min with a solution buffered to pH 6.5 or pH 8.0 (containing (mM): 90 Na, 2 K, 25 Hepes buffer, 92 Cl and ^{3}H inulin). First, the transepithelial potential difference (V_{TE}, mv) and the pH of the tubular fluid were measured at the collection site using recessed-tip pH microelectrodes (Thomas, J. Physiol. Lond. 238: 159, 1974). Second, secretion of K (J_K, pEq/min) and reabsorption of sodium (J_{Na}, pEq/min) were measured. Our results (mean values ± SEM, n=10 each group) were:

Soln.	J_K	J_{Na}	V_{TE}	pH *in vivo*
pH 6.5	-36±6	+242±38	-52±5	6.5±0.1
pH 8.0	-23±4	+265±42	-52±8	7.5±0.1

Conclusions: pH differences of 1.0 unit had no effect upon distal tubular K and Na transport. Hence, at constant luminal buffer delivery, systemic acid-base changes affect K transport by cellular and/or peritubular pH changes.

● PROSTAGLANDINS REGULATE OSMOTIC-INDUCED CHANGES IN RENIN RELEASE. J. S. Stoff, A. Cohen, K.Spokes*, P. Silva and F.H.Epstein. Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of Beth Israel Hospital, Boston, Mass.

Perfusion of the isolated rat kidney with hyperoncotic albumin abolishes filtration and stimulates renin release six-fold. Decreasing osmolality by reducing the concentration of NaCl in the perfusate prevents the increase in renin secretion induced by hyperoncotic albumin, while restoring osmolality by adding mannitol reinstitutes the increase in renin secretion. A change in volume of the juxtaglomerular cells may be responsible for these changes in renin release, but the mediator of this response is unknown. Since renal prostaglandins are important regulators of renin release, we investigated their role.

Prostaglandin appearance and renin release into the perfusate were closely correlated (R = 0.97). The concentration of PGE_2 in kidney perfusate was tripled by hyperoncotic perfusion (156±69 pg/ml → 422±129), reduced by lowering perfusate osmolality (184±51) and restored to high levels by mannitol (527±115). Renin release by hyperoncotic perfusion was markedly reduced by inhibiting prostaglandin synthesis with indomethacin.

The data suggest that variations in cell volume of the JG cells, induced by changes in oncotic or osmotic pressure, alter renin release via prostaglandins. Changes in prostaglandin synthesis might be induced by expansion or contraction of cell membranes associated with changes in cell volume.

PHARMACOLOGIC INHIBITION OF URATE TRANSPORT ACROSS PERFUSED AND NON PERFUSED RABBIT PROXIMAL STRAIGHT TUBULES. R.J. Stewart*, A.M. Chonko, (intro. by R. Huseman). Univ of Kansas Med Ctr, Kansas City, KS.

We have previously demonstrated secretion of uric acid in the proximal straight tubule (PST) of the rabbit nephron (Clin Res 23:258A, 1975) and found that urate is not absorbed to an appreciable extent in this segment (Clin Res 28:441A, 1980). To determine drug effects on transcellular urate movement, 2 mm segments of PST were perfused (4-6 nl/min) in the standard fashion. 2-^{14}C-urate was added to the rabbit serum bath and the net secretory flux determined. In all control situations net urate secretory flux exceeded 70 x 10^{-15}M/mm/min. 2 mm segments of non perfused PST were also incubated in rabbit serum containing 2-^{14}C-urate. After 60 min the tubules were rinsed, and lysed (10% T.C.A.) to release cell contents. Cell urate accumulation exceeded 350 μM in control tubules. Each experiment included PST's from 5-8 animals; the data are expressed in percent of control values.

Drug	Cell Content (10^{-3}M)	Cell Content (10^{-4}M)	Transcellular Flux (10^{-3}M)	Transcellular Flux (10^{-4}M)
Probenecid	12±3%	41±7%	---	37±9%
Sulfinpyrazone	30±3%	44±6%	---	---
P.A.H.	33±3%	68±9%	49±7%	---
Furosemide	17±5%	45±8%	---	66±6%
Pyrazinamide	70±8%	90±11%	74±12%	86±13%
Ticrynafen	56±10%	90±9%	---	---
Salicylate	---	97±8%	---	75±5%
Ouabain	10±3%	33±4%	---	30±2%

Thus, the PST is a useful model to investigate the effects of drugs on the secretory movement of urate into the urine. It appears that inhibition of transcellular urate secretion occurs in concert with decreases in cell urate concentration.

● INFLUENCE OF FLOW RATE, Na ABSORPTION, AND LUMINAL [Na] ON K SECRETION (J_K) ACROSS THE CORTICAL COLLECTING TUBULE (CCT). John B. Stokes, Dept. of Int. Med., Univ. of Iowa, Iowa City, IA.

The isolated, perfused rabbit CCT absorbs Na, secretes K and both processes are stimulated by mineralocorticoid hormone. The present studies were undertaken to examine some of the parameters likely to affect this transport system. CCT was dissected from rabbits treated with DOCA for 0-6 days. Unidirectional Na efflux (J_{Na}^{l-b}) was measured isotopically, and net Na efflux (J_{Na}) and J_K were measured by electron probe microanalysis. In the first group of 11 tubules, J_K was independent of flow rates of 3.5 to 15 nl/min. Thus, the chemical gradient for K under these conditions had little effect on J_K. In a second group of 25 tubules, transepithelial voltage (V_T), J_{Na}^{l-b}, J_{Na}, and J_K were measured simultaneously. The results show that J_K correlated with V_T (r=0.79) with the intercept at the origin; J_K correlated with J_{Na} (r=0.94) also with the intercept at the origin; and J_K also correlated with J_{Na}^{l-b} (r=0.95). Both $\Delta J_{Na}/\Delta J_K$ and $\Delta J_{Na}^{l-b}/\Delta J_K$ were 1.35, a value close to the stoichiometry for the Na-K pump in red cells. In a third series of experiments, elimination of Na from the perfusate virtually eliminated J_K. Half-maximal values of J_K appeared when perfused [Na]≈8 mEq/L, a value close to the K_m for Na transport in toad bladder. These data together with the known transepithelial K permeability are most consistent with a model for Na and K transfer occurring predominantly through the cell. This model would place a 3:2 Na-K exchanger on the basolateral membrane and ascribe to the luminal membrane a K permeability much greater than that of the basolateral membrane.

EFFECT OF VANADATE (V) ON THE FROG KIDNEY
L.P. Sullivan, J.J. Grantham and R.K. Bajaj*
Univ. of Kansas Med. Ctr., Kansas City, Ks.

The effect of V on bullfrog kidneys in which the arterial (A) and portal (P) circulations were artificially perfused at constant rates was assessed. The table shows control values and those obtained after 60 mins. of perfusion with 10^{-4}M Na_3VO_4. When infused into A, V doubled art. pressure, increased GFR and K exc. and reduced frac. Na reabsorption. When V was infused into P, GFR did not change and the changes in art. pressure, frac. Na reab. and K exc. were smaller. Tissue uptake and tubular transport was measured with the use of ^{48}V. Perfusion of A with 10^{-4}M V resulted in tissue/caval effluent ratios of 5.8±.3. With 10^{-5}M the ratio was 5.7±.4. Perfusion of P with 10^{-4}M yielded a ratio of 3.1±.3. With perfusion of A, U/P_{inf} V/Inulin ratios were 1.02±.02. Unidirectional fluxes of K were measured with the use of ^{42}K perfused into P. Arterial V increased K secretion from 0.87±.13 to 1.78±.10 µEq/min/qm d.w. This effect was not entirely due to increased urine flow since U/P K ratios rose. Unlike ouabain V did not affect K reabsorption. The results suggest that V enters cells to a greater extent and is more effective as a diuretic when applied to the luminal surface of tubules. A large component of the diuresis is due to its vascular effect.

		Art.P cm H_2O	GFR ml/min/gmdw	Frac.Na Reab.	K exc. µEq/min/gmdw
Art.	Cont.	32±1	0.84±.06	0.88±.02	1.6±.1
N=13	Exp.	59±3*	1.00±.08*	0.69±.03*	3.5±.3*
Portal	Cont.	32±1	0.58±.04	0.90±.02	1.6±.2
N=13	Exp.	43±2	0.54±.04	0.82±.02*	2.0±.2*

*p<.05

MEASUREMENT OF TRANSCAPILLARY FLUID AND PROTEIN MOVEMENT IN INTESTINE.
James J. Szwed and J.J. Friedman*. Indiana Univ., Indianapolis, IN.

Transcapillary fluid movement (FM) is the sum of changes in tissue weight (ΔFM_G), luminal secretions (ΔF_S) and lymph flows (ΔF_L). To these measured extravascular components, we compared FM derived from intravascular measurements. These intravascular measurements were calculated from changes in venous blood colloidal osmotic pressure (FM_O) which is considered to exclusively represent FM due to changes in capillary hydrostatic pressure (ΔP_C). The other intravascular measurement was FM induced by the change in the oncotic gradient ($\Delta\pi$) resulting from the increase in protein leakage (ΔPL) which occurs with histamine infusion or venous pressure elevation and is designated (ΔFM_{PL}). All values are in ml/min · 100 g expressed as means ± S.E.M. Histamine yielded the following: (N=14)

ΔFM_G ΔF_S ΔF_L ΔFM_O ΔFM_{PL}

(.21±.03)+(.022±.03)+(.03±.01)=(.13±.02)+(.11±.02)

.26±.04=.24±.02

Venous pressure elevation (20 mmHg) gave these results: (N=21)

ΔFM_G ΔF_S ΔF_L ΔFM_O ΔFM_{PL}

(.27±.04)+(.02±.01)+(-.018±.011)=(.16±.02)+(.10±.04)

.27±.05=.26±.05

These studies show agreement between measured and estimated FM during venous pressure elevation and with increased permeability due to histamine infusion. This study validates the usage of the sum of FM_O and FM_{PL} as a measure of transcapillary fluid movement. Since FM_{PL} is dependent on transcapillary protein leakage (TT) and venous blood protein concentration, TT can be calculated without resort to radionuclides. Therefore, FM and TT can be measured easily and continuously in clinical settings.

EFFECTS OF IODOACETATE AND LYSINE ON TUBULAR ABSORPTION OF β_2 MICROGLOBULIN (β_2M) AND CYTOCHROME C (CYT C) IN THE ISOLATED PERFUSED RAT KIDNEY (IPRK).
B. E. Sumpio*, S. S. Tate*, and T. Maack, Departments of Physiology and Biochemistry, Cornell Univ. Medical College, New York, N. Y.

Renal handling of human β_2M and ^{14}C-methylated CYT C by the IPRK was studied by formerly described techniques (Maack et al., Kidney Int. 16: 251, 1979) to determine factors affecting tubular absorption (T) of small proteins. CYT C and inulin radioactivity, β_2M immunoreactivity, and [Na] were measured in perfusate and urine. The glomerular sieving coefficients of β_2M and CYT C were .94 ± .10 (n=5) and .65 ± .20 (n=3), respectively. In control conditions T_{β_2M} and $T_{CYT\ C}$ were more than 95% of their filtered loads. Iodoacetate (10 mM) almost completely inhibited T_{β_2M}, $T_{CYT\ C}$, and T_{Na}. Lysine (5 mM) inhibited $T_{\beta_2 M}$ by 71 ± 10% (n=5) of control but had no significant effect on $T_{CYT\ C}$, T_{Na} and GFR. Electronmicrographs of lysine treated IPRK showed marked shortening and disruption of the brush border in the initial segment of the proximal convoluted tubule (PCT). Glomerular and proximal tubule morphology of control IPRK was normal. The results show that factors which interfere with metabolic energy supply and endocytosis, such as iodoacetate, affect tubular absorption of both proteins while lysine, which selectively causes lesions in the initial portion of the PCT affects preferentially $T_{\beta 2M}$. It is concluded that β_2M is probably absorbed preferentially in the initial portions of the PCT and therefore may be a sensitive marker of abnormalities of this nephron segment.

AXIAL HETEROGENEITY OF TRANSMEMBRANE ELECTRICAL POTENTIAL IN ISOLATED PROXIMAL RENAL TUBULES.
D.A. Terreros,* J.A. Grantham,* M. Tarr,* and J.J. Grantham, Univ. Kansas Med Ctr., Dept of Physiol. & Medicine, Kansas City, Kansas.

We have recently developed a method for measuring the transmembrane electrical potential (PD) of proximal tubules isolated from rabbit kidneys with collagenase. The mean PD measured across basolateral cell membranes of non-perfused random convoluted tubules was -29 mV. To determine the PD in specific segments we dissected superficial S_1, S_2 and S_3 portions and bathed them in collagenase long enough to weaken the basement membrane. Cells were impaled with Ling-Gerard microelectrodes. Tubules from 5 animals were studied in rabbit serum at 37°C, approximately 6 impalements per tubule. The mean PD was: S_1 segments (82 cells), -46.3 ± 1.5 mV; S_2 segments (59 cells), -27.2 ± 1.0 mV; S_3 segments (59 cells), -17.1 ± 1.1 mV, the differences among the segments being highly significant. We conclude that the transmembrane PD of proximal cells decreases progressively from glomerulus to loop of Henle. These changes in PD mimic the well-established pattern of sodium and water reabsorption along superficial proximal tubules.

DISTRIBUTION OF MOLECULAR WEIGHT MARKERS IN THE POSTGLOMERULAR CIRCULATION - EFFECT OF EXCLUDED VOLUME AND PERMEABILITY BARRIER. C. Trainor* and M. Silverman. Dept. of Medicine, Univ. of Toronto, Toronto, Ontario.

The intrarenal distribution of various molecular weight markers was studied using the pulse injection indicator dilution technique in anesthetized mongrel dogs. Simultaneous renal vein and urine outflow curves were obtained for T1824-albumin (plasma reference), creatinine (extracellular reference) and the following test substances: ^{3}H-raffinose (mol. wt. 594), ^{3}H-vitamin B (mol. wt. 1355), and ^{14}C-inulin (mol. wt. $\sim$ 5,000). The urine outflow curves for all test indicators superimposed on simultaneously injected creatinine. We used a permeability barrier model (Goresky, Ziegler and Bach, Circ. Res. 27:739-764, 1970) to analyze the renal vein outflow curves. The solution was programmed on a VAX minicomputer, and three parameters were adjusted to yield the best fits for each indicator: large vessel transit time; permeability of the barrier between vascular and interstitial spaces; and the ratio of interstitial to vascular volumes. The results show that with increasing molecular size from creatinine to inulin, permeability decreases; in addition the ratio of interstitial to vascular volume decreases and this excluded volume effect is accentuated by mannitol diuresis relative to hydropenia. A combination of excluded volume plus permeability limitation in the postglomerular circulation makes it likely that postglomerular extraction of indicator probes > 10 - 15 x 10^3 daltons approaches zero. Thus the single pass pulse injection technique may prove useful to study in vivo glomerular extraction of substances in the range 15 - 70,000.

EFFECT OF PHENTOLAMINE (P) ON GLOMERULAR DYNAMICS INACTIN (I) AND α-CHLORALOSE (α-C) ANESTHETIZED RATS. Bryan J. Tucker,*, Orjan W. Peterson,* and Roland C. Blantz, Univ. of Calif., San Diego, La Jolla, CA and VA Medical Center, San Diego, CA.

P, an α-adrenergic antagonist, was utilized in two groups of Munich-Wistar rats, one group (n=6) was anesthetized with I and the other group (n=6) anesthetized with α-C to determine if the α component of the sympathetic nervous system affects the glomerular dynamics during I anesthesia. Micropuncture techniques were utilized to measure nephron filtration rate (sngfr), nephron plasma flow (rpf), glomerular hydrostatic pressure gradient (ΔP), and afferent (AR) and efferent (ER) arteriolar resistances. Mean arterial pressure (MAP) and glomerular filtration rates (GFR) were also measured in both a control hydropenic (C) and during administration of P (27 μg/kg BW/min). The results are as follows: (†=p<0.05 from I(C), *=p<0.05 compared to α-C(C)).

	MAP mm Hg	sngfr nl/min	rpf nl/min	ΔP mm Hg	AR [dynes·sec·cm^{-5}]	ER
I(C)	114±3	38±2*	115±12*	34±0.6*	22±3	12±2
I(P)	86±1†	30±1†	92±4†	31±0.7†	18±1	12±1
α-C(C)	105±7	31±1†	93±5†	31±0.6†	23±3	11±1
α-C(P)	94±3†*	31±2†	93±10	30±0.8†	22±2	13±2

GFR decreased after P in I anesthetized rats (p< 0.01) but did not decrease in α-C. Filtration pressure equilibrium persisted in all periods indicating that glomerular permeability was not a factor in alterations of sngfr. Conclusions: Although sngfr, rpf and ΔP are higher in I(C) compared to I(P) and α-C(C&P) there is no difference in AR and ER indicating that I increases only nonrenal α-adrenergic activity and changes in glomerular dynamics may be due to MAP effects.

● ADH-DEPENDENT NEPHRON HETEROGENEITY IN RATS WITH HEREDITARY HYPOTHALAMIC DIABETES INSIPIDUS. M.M. Trinh-Trang-Tan*, J.P. Grünfeld* and Lise Bankir* (intr. by H. Valtin), INSERM U90, Hosp. Necker, F-75730 Paris Cedex 15, France.

Single nephron glomerular filtration rate (SN GFR), glomerular volume (GV) and proximal tubular length (PTL) were measured by the ^{14}C Na ferrocyanide infusion technique in superficial (S) and juxtamedullary (JM) nephrons of anesthetized Brattleboro rats with (DI) and without (HZ) diabetes insipidus. The well-known nephron heterogeneity (heter) was absent or greatly reduced in DI as compared to HZ, due to reduced filtration and dimensions in JM nephrons. Daily s.c. injections in DI rats of the vasopressin analogue dDAVP from 2 to 8-10 wks of age (TDI) significantly increased values in JM nephrons and restored a nearly normal nephron heterogeneity (see Table).

	n	SNGFR, nl/min			GV	PTL
		S	JM	S/JM	S/JM	S/JM
HZ	4	36±4	52±7†	.71±.04	.50±.03	.73±.03
DI	6	34±4	32±3*	1.04±.04*	.77±.03*	.90±.04*
TDI	6	33±4	42±2*†	.78±.03*	.59±.02*	.78±.02*

(Means±SEM. † or *, p<0.05 or less; † = S vs JM; * = DI vs HZ or TDI vs DI). A significant correlation was observed between SNGFR heter (S/JM ratio) and urine flow rate. In addition we and others have reported accentuated nephron heter in desert rodents with high urine concentrating ability. These results suggest that anatomical and functional nephron heter is dependent upon the presence of antidiuretic hormone and/or concentrating ability. These factors selectively increase size and filtration in deep nephrons.

● EFFECT OF LUMINAL CHLORIDE CONCENTRATION ON POTASSIUM SECRETION BY RENAL DISTAL TUBULE. Heino Velázquez*, Fred S. Wright and David W. Good*. Yale Univ Sch of Med and VA Med Ctr, New Haven CT

We have shown recently (Fed.Proc.39:1079, 1980) that substituting sulfate for chloride in distal tubule fluid increases net potassium secretion. To determine whether this increase is caused by addition of SO_4 or removal of Cl, in vivo microperfusion experiments were performed on adult Sprague-Dawley rats. Superficial distal tubules were perfused at 16 nl/min and paired samples were obtained from each tubule. Two perfusion solutions were used: I, resembled normal early distal fluid (Na 75 mM, K 2 mM) except that all Cl was replaced by 34 mM SO_4; II, consisted of Soln. I plus 40 mM NaCl. Total solute concentration was adjusted (with 140-187 mM urea) to reduce net fluid absorption to zero. Ion concentrations in collected fluid ([i], mM), net ion fluxes (J_i, pmol/min, negative values indicate secretion), and transepithelial voltage (V_{TE}, mV) were:

Soln.	[Na]	[K]	[Cl]	J_{Na}	J_K	J_{Cl}	V_{TE}
I	70	8.8	8.1	60	-108	-131	-46.1
II	98	7.2	35	255	-85	65	-45.1

Raising [NaCl] while keeping [SO_4] constant increased Na absorption, reversed net Cl transport, reduced net K secretion (P<.001 for each) and reduced V_{TE} (P<.05). Increasing Na absorption would not be expected to decrease K secretion; previous results indicate that the 1 mV decrease in V_{TE} is not sufficient to account for the 21% decrease in K secretion. We postulate that increasing luminal [Cl] may increase the absorptive fluxes of both Cl and K. The higher rate of net K secretion seen with the Cl-free solution may be the result of a lower backflux of K from the lumen.

● CHLORIDE TRANSPORT PATHWAYS IN BRUSH-BORDER VESICLES. D.G. Warnock and V.J. Yee*. CVRI & Dept. Medicine, Univ. Calif., San Francisco, CA.

Recent studies of brush-border membrane vesicles (BBMV) have suggested that there may be 2 mechanisms for chloride ($36Cl^-$) uptake: 1) coupling to inwardly-directed H^+ gradients, and 2) coupling to K^+ gradients in the presence of valinomycin (VAL) (Fed. Proceed.39:734, 1980). The present studies examined the anion specificities of the $36Cl^-$ uptake pathways. BBMV were prepared from rabbit renal cortex by divalent cation precipitation. $36Cl^-$ uptake was measured at 60 sec with a rapid filtration assay. External media contained 20 mM K36Cl, and either 80 mM KCl, KSCN, KNO_3, KAcetate or 40 mM K_2SO_4. pH in = pH out = 7.5 for the K^+ gradient studies. pH in = 7.5, pH out = 6.0, and K^+ in = K^+ out for the H^+ gradient studies. The competitive effect of anions on $36Cl^-$ uptake was expressed as % uptake, relative to the effect of unlabelled chloride.

	Cl^-	SCN^-	NO_3^-	Acetate	$SO_4^=$
K^+ Gradient plus VAL (K^+ out > K^+ in)	100%	88% ± 4	97% ± 4	124% ± 4	171% ± 4
H^+ Gradient (H^+ out > H^+ in)	100%	111% ± 5	107% ± 4	121% ± 6	145% ± 25

SCN^- effectively competed for $36Cl^-$ uptake in the conductive mode (K^+ gradient plus VAL). This anion permeability sequence is identical to that predicted from the effects of permeable anions on electrogenic sodium co-transport ($SCN^- > NO_3^- > Cl^- > SO_4^=$). Conclusions: 1) The anion competition studies demonstrate 2 distinct pathways for $36Cl^-$ uptake into BBMV. 2) SCN^- does not effectively compete for $36Cl^-$ uptake in the H^+-driven mode, implying that $36Cl^-$ uptake is not electrically-coupled to the H^+ gradient. 3) Acetate does not strongly compete for $36Cl^-$ uptake in the pH range of 6.0 to 7.5.

● HETEROGENEITY OF URIC ACID TRANSPORT IN PROXIMAL TUBULES. J.L. Weber*, J.P. Kokko, H.R. Jacobson. U. Texas Hlth. Sci. Cntr., Dallas, Texas.

Mammalian proximal tubules are known to both reabsorb and secrete uric acid. However, the relative contribution of either process to net uric acid reabsorption in the various anatomic regions of proximal tubules is unknown. The present in vitro microperfusion studies of rabbit tubules utilize ^{14}C uric acid and chemical measurements of uric acid via high pressure liquid chromatography to determine simultaneously both unidirectional and net uric acid fluxes. Superficial (SFPCT) and juxtamedullary (JMPCT) convolutions and superficial pars recta (SFPR) were perfused with serum ultrafiltrate and bathed in serum at 37°C and pH 7.4 (uric acid 3.6 mg% in both solutions). Net, lumen to bath (Flux L→B), and bath to lumen (Flux B→L) fluxes are listed below.

	Net flux	Flux L→B	Flux B→L
	(pgm/mm.min)		
SFPCT	-50.9±14.2*¶	6.6±1.3*	57.9±14.1*
JMPCT	11.3±2.9§	16.9±3.6	4.0±3.6§
SFPR	-16.7±3.5	9.3±1.2	26.1±4.0

$p<0.05$ * SFPCT v JMPCT ¶ SFPCT v SFPR § JMPCT v SFPR

We conclude: 1) Inter and intranephron heterogeneity exists in proximal tubule uric acid transport. SFPCT and SFPR exhibit net secretion, the former to a greter extent. JMPCT exhibit net reabsorption. 2) While significant bidirectional transport exists in all segments, the major determinent of net transport is the presence or absence of a large amount of secretion. 3) Further evaluation of renal uric acid transport requires consideration of heterogeneity.

● NET K^+ SECRETION IN PROXIMAL STRAIGHT TUBULES (PST). A.G. Wasserstein*, and Z.S. Agus, Dept. of Med., Univ. of Pa. Med. School, Phila., Pa.

Net K+ secretion has been shown prior to the hairpin turn of Henle's loop (Jamison et al, KI 9:323, 1976) but its exact site and characteristics remain uncertain. We perfused rabbit superficial PST in vitro with standard (Puf) or late proximal (Pp) perfusates containing 5 mEq/L K+, differing in Cl, HCO3, and organic solutes. Outer cortical (S2) and medullary (S3) PST were distinguished anatomically. Fluid absorption (Jv) was measured with 3H-inulin and K+ with electron probe.

In S3, perfusion rates (Vi) were 6.35±0.57 and 7.33±0.75 nl/min (NS) and Jv 0.41±0.07 and 0.57±0.06 nl/mm/min (NS). There was significant net K secretion with Jk -1.73±0.59 and -3.78±0.75 pEq/mm/min ($p<0.05$) in Pp (n=7) and Puf (n=15), respectively. K+ secretion was abolished by ouabain (0.54±0.44 and 0.25±0.59 in Pp and Puf, respectively, $p<0.05$ vs control). Collected/bath K+ concentration ratios were 1.17 (Pp) and 1.32 (Puf), higher than predicted from previously reported PD. Puf-perfused S2 segments also showed ouabain-sensitive K+ secretion but Jk was significantly less than in S3 and 3/10 tubules showed K+ reabsorption. Jk was correlated with Vi in all tubules (r=0.36), particularly in Pp (r=0.92). PAH, 0.5-1.0 mM in bath had no significant effect on Jk in either segment.

We conclude that net K+ secretion occurs in S2 and S3 of superficial PST and is 1) probably active, 2) ouabain-sensitive, 3) flow-dependent, 4) augmented by perfusate resembling ultrafiltrate, and 5) not dependent on organic acid secretion.

● DETERMINATION OF THE TRANSPORT CONSTANTS FOR URATE ABSORPTION IN THE RAT PROXIMAL TUBULE. E.J. Weinman, S.C. Sansom,* H.O. Senekjian, and T.F. Knight. VA Med. Ctr and Baylor Coll. Med., Houston, Texas.

Proximal convoluted tubules were microperfused in vivo at a constant rate of 20 nl/min with solutions containing radioactive 2-^{14}C urate in varying concentrations. The perfusion solution was either a steady-state equilibrium solution or a water-absorbing solution. With both perfusion solutions, there was a positive relationship between the flux of urate and the mean intraluminal urate concentration, but there was no significant difference between the two perfusion solutions. No evidence of saturation of absorption was obtained. The passive permeability of urate determined from solutions with high urate concentrations was 0.68 pmol/min/mm/mM. After correction of the net flux of urate for the contribution of passive permeation, the apparent Km was 0.17 mM and the Vmax 0.31 pmol/min/mm.

The reflection coefficient for urate was determined by simultaneously microperfusing the peritubular capillary and tubular lumen with solutions containing p-chloromercuribenzoate. The capillary solution was either isotonic to the luminal solution or made hypertonic by the addition of raffinose (50 mOsm/kg H_2O). The reflection coefficient was similar with both solutions and averaged 0.94.

These findings are the first determination of the transport constants of the active component of urate absorption in the rat proximal tubule. They confirm prior estimates of the diffusional permeability of urate and further indicate that solvent drag is not a major determinant of urate absorption.

MORPHOMETRIC ANALYSIS OF CELLS AND EXTRACELLULAR CHANNELS IN CONNECTING TUBULE (CNT) OF RABBIT. Larry W. Welling and Dan J. Welling, Laboratory Service, VA Medical Center, Kansas City, Missouri, and Depts. of Pathology and Physiology, Univ. of Kansas Medical Center, Kansas City, Kansas

Computer assisted morphometric procedures were used to measure from transmission electron micrographs the surface membrane concentrations, S_V, of connecting tubule cells (CC) and of intercalated cells (IC) in 18 CNT transverse sections. S_V of all lateral cell membranes (TLM) was calculated for the whole tubule wall and for 5 cellular zones each representing 20% of cell height. TLM was divided further into those membranes (LM) facing lateral intercellular channels between adjacent cells and those membranes (IM) facing basal infolded channels. S_V in CC were TLM = 1.60 ± 0.10, LM = 0.36 ± 0.02, and IM = 1.24 ± 0.10. For IC, TLM = 0.37 ± 0.03, LM = 0.28 ± 0.02, and IM = 0.09 ± 0.02. Thus, 78% of lateral cell membrane in CC faces basal infolded channels while only 24% of lateral membrane in IC faces infolded channels. In the 5 cellular zones of CC the S_V of LM is relatively constant while the S_V of IM increases exponentially from 0.55 ± 0.08 near the cell apex to 2.04 ± 0.15 near the cell base. In IC the S_V of LM also is constant through the zones but IM is present only in the basal 20%. In both cell types the area of LM represents a 2-fold enlargement of the lateral channel surfaces by small microvilli. The extensive, exponential, infolded channels in CC are reminescent of all channels in proximal tubules. The dimensions of CC and IC in CNT are very similar to those of the principal and intercalated cells, respectively, of rabbit cortical collecting duct.

UREA REABSORPTION IN THE MEDULLARY COLLECTING DUCT (MCD) IN RATS ON A LOW PROTEIN DIET BEFORE AND DURING UREA INFUSION. D.R. Wilson and H. Sonnenberg. Depts. of Medicine and Physiology, University of Toronto, Toronto, Canada.

The changes in MCD function during urea-induced enhancement of urine concentrating ability have not been determined. In 6 young rats on a low protein diet, MCD function was studied by microcatheterization before and during urea infusion which raised the plasma urea level from 3.0 to 10.3 mM/l. Urea infusion increased urine osmolality and non-urea solute concentration ($p<0.05$). Before urea infusion, the remaining fraction of filtered urea (FR urea=TF/P urea/inulin) decreased from 0.47 to 0.23 between the beginning and end of the MCD in 18 paired samples ($p<0.001$). During urea infusion FR urea decreased from 0.58 to 0.34 along the duct ($n=18$, $p<0.001$). Although these changes in FR urea along the MCD before and during urea infusion were not different, the increase in filtered urea load and fractional delivery to the duct during urea infusion resulted in a 3-fold increase in absolute urea reabsorption along the MCD.

Conclusions: 1) Urea reabsorption along the MCD was increased in rats on a low protein diet before urea infusion, compared to our previous study of normals (Kidney 16, 838, 1979).
2) Increased urea reabsorption along the MCD after urea infusion was associated with increased urine osmolality and non-urea solute concentration.
3) The urine to papillary interstitial urea concentration gradient was also increased after urea infusion, favouring passive urea reabsorption.

TUBULAR SECRETION OF NOREPINEPHRINE RELEASED FROM RENAL NERVES. Lynn R. Willis, Rodney W. Lappe,* David P. Henry* and Anthony R. Terzian*. Indiana Univ. Sch. of Med., Dept. of Pharmacol., and Eli Lilly and Co., Indianapolis, Indiana

The relationship of the renal nerves (RN) to the urinary excretion (UV) of norepinephrine (NE) has not been characterized. Urinary NE may be an index of circulating levels of NE or of the level of activity of the RN. These studies examined the fate of NE released from RN of anesthetized rabbits. Electrical stimulation (S) of RN (4 Hz, 5V, 0.5 msec) in 9 untreated (U) and 5 treated rabbits (cyanine 863 [Cy], 6mg/kg) evoked these results:

	V		GFR		$U_{NE}V$	
	C	S	C	S	C	S
U	203±10	178±12*	2.4±0.2	1.8±0.2*	5.1±0.7	8.3±1.6*
Cy	161±8	154±12	1.6±0.3	1.3±0.3*	2.1±0.4	1.7±0.3

V = urine flow, µl/min; GFR = inulin clearance ml/min; $U_{NE}V$ = ng/min/ml GFR. *$p<0.05$.

The reductions in GFR in both groups were not significantly different from each other. C_{NE}/GFR was 4.0±0.4 before (C), and 6.2±0.9 after RNS ($p<0.05$) in the untreated group, and 1.9±0.3 and 1.6±0.3 (NS) in the Cy group. Values after Cy were significantly different from corresponding U values. In other experiments, the excretion of ^{3}H-NE released from post-glomerular RN in the renal corticis (labelled by surface application of ^{3}H-NE) by tyramine (T) (10^{-3}M) was inhibited by Cy but not by probenecid (100mg/kg). The data demonstrate that 1) NE released from renal nerves by stimulation or tyramine was excreted largely by cationic tubular secretion and, 2) post-glomerular as well as pre-glomerular renal nerves contribute to the excretion of NE.

● ACTIVE K SECRETION BY THE CORTICAL COLLECTING TUBULE (CCT) OF ADRENALECTOMIZED RABBITS. C.S. Wingo, W.E. Lombard, J.P. Kokko, H.R. Jacobson Univ. of Tx Health Science Ctr., Dallas, Texas.

It is known that Addisonian and adrenalectomized individuals are capable of enhanced potassium excretion when challenged with an increased load. To examine whether the CCT contributes to this phenomenon, CCT from chronically K loaded adrenalectomized rabbits were perfused in vitro. Rabbits were adrenalectomized and allowed to recover 7 days before sacrifice while maintained on glucocorticoid replacement (50 µg/day dexamethasone) and high K diet. (9 meq K/kg body weight). Tubules were perfused and bathed with artificial ultrafiltrate simulating plasma. Potential difference (PD), volume reabsorption, and K concentrations of perfused and collected fluid (via helium glow photometry) were measured. The mean values ± SEM for perfusion rate (V_i in nl/min), perfused and collected [K] in meq/L, observed PD in mV lumen with respect to bath, and the calculated equilibrium potential PDeq assuming passive K distribution are listed below.

Vi	Collected [K]	Perfused [K]	PD	PDeq
1.47±.21	16.5±2.6	5.6±0.3	-5.9±2.3	-29.9

Net K secretion was 5.5±0.8 peq/mm min. We conclude 1) CCT of K loaded adrenalectomized rabbits actively secrete K. 2) This K secretion, independent of mineralocorticoid, may play a role in K homeostasis of Addison's disease.

● POTASSIUM TRANSPORT IN SUPERFICIAL AND JUXTAMEDULLARY PROXIMAL STRAIGHT TUBULES. Jack Work,* Susan L. Troutman* and James A.Schafer. Nephrology Center, Depts. of Med. and Physiol., Univ. of Alabama in B'ham, Birmingham, AL 35294

Transport of K^+ was examined in superficial (S) and juxtamedullary (JM) rabbit proximal straight tubules perfused and bathed at 38°C with standard HCO_3^- buffers. Unidirectional lumen-to-bath (J^{lb}, pmol min^{-1} mm^{-1}) and bath-to-lumen (J^{bl}) fluxes of $^{42}K^+$ and $^{86}Rb^+$ (as a K^+ analog) were measured. In S segments at 5 mM Rb^+, the ^{86}Rb-J^{lb} was 5.35 ± 0.64 (SEM) which was not significantly different from the J^{bl} of 5.89 ± 0.63. Neither flux was altered by 0.1 mM ouabain nor by prior in vivo K^+-loading or depletion, and both were identical to corresponding ^{42}K fluxes. J^{lb} and J^{bl} for ^{86}Rb showed a linear relation to the Rb^+ concentration giving a permeability coefficient of 0.17 µm/sec. Both ^{42}K and ^{86}Rb fluxes were markedly higher in JM segments: for ^{86}Rb, J^{lb} was 12.08 ± 1.89 and J^{bl} was 15.78 ± 1.69, giving a permeability of 0.6 µm/sec. Neither flux was altered by K^+ loading or depletion. A model of K^+ transport in these segments shows that the K^+ permeability of S segments would allow continued absorption with a rising luminal K^+ concentration which could reach a maximum only 50-80% above the plasma concentration. In the outer medulla, the high K^+ permeability of JM segments would allow rapid K^+ entry if the medullary interstitial K^+ concentration were elevated. For example, passive K^+ entry from an interstitial concentration of 15 mM would give 80% equilibration within the JM segments. These results are consistent with the hypothesis of Jamison et al (Kid. Int. 9:323, 1976) that the first important site of K^+ secretion may be different in S and JM nephrons.

URINARY ELECTROLYTE EXCRETION (UEV) IN THE SPONTANEOUSLY HYPERTENSIVE RAT (SHR): RESPONSE TO PARATHYROIDECTOMY (PTX). Nam N. Yung,* Beth A. Ugoretz,* and David A. McCarron (intr. by Edmond Braun). Univ. of Oregon Hlth. Sci. Ctr., Div. of Nephrol., Portland, Oregon.

Reports in human and experimental hypertension have suggested that parathyroid hormone (PTH) may influence UEV differentially where arterial pressure is increased. We measured urinary Na (UNaV), K (UKV) and UCaV, pre-PTX, 3-6 days after PTX and 4 weeks after Ca repletion with a 4% Ca diet. Eight SHR and five Wistar-Kyoto (WKY) normotensive rats had PTX.

After PTX, serum ionized calcium (Ca++) declined ($p<.001$) similarly in both strains. The 4% Ca diet normalized the serum Ca++ ($p<.001$) of the SHR- and WKY-PTX. SHR's UCaV was greater ($p<.01$) pre-PTX while UNaV and UKV were similar in both strains. After PTX, UCaV fell in the SHR ($p<.01$) as the serum Ca++ and filtered Ca load declined, but was unchanged in the WKY. With Ca repletion, UCaV increased ($p<.001$) in both SHR- and WKY-PTX animals. UNaV fell after PTX ($p<.001$) in both SHR and WKY. The SHR's UNaV returned to pre-PTX values with Ca repletion while the WKY's UNaV actually rose ($p<.05$) above pre-PTX levels. UKV declined in the SHR ($p<.001$) after PTX but was unchanged in the WKY. 4% Ca diet returned UKV to pre-PTX levels in the SHR, while the WKY's UKV increased above pre-PTX levels ($p<.005$).

In summary: 1) UCaV, UNaV and UKV respond differently in the SHR versus WKY after PTX; 2) UNaV and UKV of the SHR appear to be more PTH-dependent than in the normotensive WKY; 3) these findings suggest a beneficial role for PTH in the maintenance of Na and K balance in the SHR.

SENSITIVITY ANALYSIS OF FACTORS AFFECTING STEADY STATE POTASSIUM EXCRETION. David B. Young. Univ. of Mississippi Medical Center, Dept. of Physiology and Biophysics, Jackson, MS 39216.

Steady state renal K excretion is affected by plasma K concentration (P(K)), plasma aldosterone concentration (aldo) and the rate of Na intake. The present analysis was undertaken to determine quantitatively the sensitivity of K excretion to changes in these three variables. Data were obtained from experiments carried out in adrenalectomized dogs maintained for several months with controlled rates of aldosterone replacement and Na and K intakes. Daily rates of K excretion were determined by collection from the metabolic cages in which the dogs were housed. The three independent variables were changed separately; while one was changed the other two were fixed at normal levels. The normal levels for the dogs were: P(K)=4.0 mEq/L; aldo = 50 µg/day infused i.v.; Na intake = 30 mEq/day. The variables were held constant for 10 days by which time the dogs were in a steady state of electrolyte balance. Only steady-state data were used in this analysis. Increasing P(K) above the normal point results in a 53% increase in K excretion for each 1% increase in P(K); increasing the aldosterone infusion rate results in 0.6% change in K excretion for each 1% change in aldosterone; increasing Na intake results in a 0.3% change in K excretion for each 1% change in Na intake. The results demonstrate the powerful effect of P(K) on K excretion which is approximately an order of magnitude greater than the effects of aldosterone and Na intake.
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EFFECT OF OSMOLALITY ON BRADYKININ-MEDIATED INCREASES IN RENAL SLICE PROSTAGLANDIN E_2 SYNTHESIS. T.V. Zenser, N.S. Rapp, E.S. Davis and B.B. Davis. VA Medical Center, St. Louis, Missouri.

Renal inner medullary (IM) solute concentration is a physiological parameter which might effect IM function. The effect of solute concentration on IM PGE_2 production was evaluated by incubating slices in Krebs buffer (KB) with and without addition of various solutes. PGE_2 synthesis was determined by RIA. In KB basal PGE_2 was 2.9 ± 0.3 and increased to 7.5 ± 0.8 ng/mg wet weight with bradykinin (BK). Addition of 0.5 M NaCl had no effect on basal (3.0 ± 0.6) but inhibited BK (4.2 ± 0.5). Mannitol (1.0 M) increased basal (5.4 ± 0.6) but there was no effect of BK (6.5 ± 0.7). Urea caused a dose dependent decrease in BK stimulation from 7.5 ± 0.8 in KB to 4.8 ± 0.7 at 0.1 M, 3.6 ± 0.5 at 0.3 M, 1.8 ± 0.3 at 0.6 M, 1.0 ± 0.2 at 0.8 M and 1.3 ± 0.5 at 1.0 M urea. Basal PGE_2 synthesis was not significantly reduced until 0.8 M urea (1.4 ± 0.3). In contrast to BK, arachidonic acid-mediated increases in PGE_2 synthesis were not reduced by urea. With KB, 0.5 mM arachidonic acid increased PGE_2 from 2.3 ± 0.3 to 16.0 ± 0.8. With 1.0 M urea, arachidonic acid increased PGE_2 from 0.9 ± 0.2 to 14.5 ± 1.1. Thus, all solutes tested inhibited BK-induced increases in PG production. The data suggest changing IM urea concentration may modulate agonist-induced increases in PG production. The mechanism of urea inhibition appears to be prior to cyclooxygenase. The differential effects on basal and BK suggests an inhibition by urea at a hormone sensitive step.

Transplantation

UNUSUAL RENAL TRANSPLANT REJECTIONS IN RECIPIENTS OF PRE-TRANSPLANT, DONOR-SPECIFIC TRANSFUSIONS. William Amend, Flavio Vincenti, Nicholas Feduska*, Deanne Hanes*, Susan Hopper*, Oscar Salvatierra; Univ. of Calif., Transplant Service, San Fran.,CA.

Thirty two one-haplotype related recipients undergoing pre-renal transplant (TX) donor-specific transfusions (DSTs) were evaluated regarding post-TX rejection (rej.). All 32 were highly reactive (MLC>8) to their donors. Serial post-transfusion sera had revealed neither warm-B nor T-cell antibodies to the donor.

Uncharacteristic early rejs. were noted in 10/32. These 10 episodes occurred quite early (3-7d post TX), were variably severe (Creat. rises of 0.7-5.2 mg%), yet all showed resolution over 5-14d. By comparison, in 174 unmodified cad. TX and 70 related TX with 1st wk. rej., 51% & 36% were lost by 3 mo.

	NO EARLY REJ.	EARLY REJ.
No. of patients (n)	22	10
Long-term function (n)	22	9*
Duration-transplant	6-26 mo.	1-23 mo.
Creatinine (mg%)	1.3 ± 0.55	1.7 ± 0.46
(*1 - TX loss 2° to discontinuance meds.)		
3rd party transfusion (n)	14	6
M.L.C.	8-40	8-55
Donor Cold-B (n)	4	3
>10% panel-reactivity		
Warm-B (n)	9	5
Warm-T (n)	2	2

Two pts. had TX biopsies; both had vascular changes. No TX in 6 children has had an early reject. CONCLUSION: The accelerated-type rejs. in DST-TXs have an unexpectedly benign prognosis and probably have a different pathogenetic mechanism than the frequently irreversible accelerated rejs. in unmodified TX recipients.

ACTIVE UPTAKE OF PARA-AMINO-HIPPURATE (PAH), N-METHYLNICOTINAMIDE (NMN) AND GENTAMICIN (G) BY HUMAN RENAL CORTEX AFTER PROLONGED COLLINS-2 PRESERVATION. William M. Bennett, W. Clayton Elliott, and John M. Barry. Univ. of Oregon Hlth. Sci. Ctr., Divs. of Nephrol. and Urol., Portland, Oregon.

There has been reluctance to transplant kidneys preserved for over 24 hours in Collins-2 solution because of the possibility of tubular damage. To evaluate proximal tubular function after 34-50 hours of Collins-2 preservation, we determined active uptake of PAH, NMN and G by renal cortical slices from four cadaver donors whose kidneys were not utilized for transplantation. Slices were incubated for 90 minutes in modified Cross and Taggart media at 25°C under 100% O_2 in the presence of PAH, NMN and G. Uptake was expressed as slice to media ratio (SM). The active component of uptake (SMA) was defined as the difference in SM's of experimental slices and control slices metabolically inhibited with iodoacetate.

Age/Sex	Hr*	PAH SM	PAH SMA	NMN SM	NMN SMA	G SM	G SMA
1 24/M	50	8.62	7.18	2.02	.73	4.44	1.63
2 5/M	34	3.54	2.49	.79	-.11	5.44	1.62
3 27/F	36	7.60	6.19	2.81	.93	4.21	1.10
4 48/M	36	5.76	4.75	3.43	1.91	5.76	1.07
x± SD		6.38± 2.23	5.15± 2.04	2.26± 1.14	.865± .83	4.96± .75	1.36± .31

*Hours of Collins-2 preservation

We conclude that: 1) human kidneys preserved for long periods in Collins-2 media retain substantial proximal tubular function, and 2) active NMN uptake may be more profoundly depressed than PAH or G uptake after long preservation.

● INSULIN RELEASE, INSULIN BINDING AND GLUCOSE TOLERANCE IN RENAL TRANSPLANT RECIPIENTS (TR). William Briggs, Stephen Migdal, Sudesh Mahajan*, Franklin McDonald, Wayne State University, Detroit, Michigan.

Although glucose intolerance is a recognized accompaniment of uremia, little is known regarding glucose tolerance in TR. Thus, intravenous glucose tolerance tests (IVGTT) and studies of ^{125}I-insulin binding (†IB) to peripheral blood monocytes were done in 8 TR and 7 control subjects (CS). One TR had fasting hyperglycemia, elevated Hb A1C and abnormal IVGTT. Comparisons (mean ± SEM) between 7 TR with normal glucose tolerance and 7 CS showed:

	TR	CS	p
Fasting Blood Glucose (mg/dl)	93±3	90±3	NS
Hemoglobin A1C (%)	7.2±0.4	6.1±0.4	NS
Fasting Insulin (μU/ml)	27±2	27±2	NS
Fasting Glucagon (pg/ml)	256±40	231±46	NS
Fasting Growth Hormone (ng/ml)	9.5±2.6	2.2±0.8	0.03
Insulin AUC§ during IVGTT	3934±532	2346±266	0.02
Glucose decay constant	2.48±0.32	2.13±0.22	NS

§AUC=area under curve, plasma concentration vs. time

Plasma glucagon and growth hormone were appropriately suppressed during IVGTT in TR as in CS. Percent specific †IB was significantly higher in TR than CS (9.7±0.9 vs. 7.0±0.8, p=0.04); this was associated with a significant increase in maximal binding capacity of TR cells. Conclusion: Despite chronic steroid therapy, 7/8 TR had normal glucose tolerance. Steroid therapy in TR resulted in significantly enhanced insulin release during IVGTT and significantly increased numbers of insulin receptors on monocytes.

● ALLOGRAFT PROLONGATION WITH POLYAMINE ENZYME INHIBITOR, RMI 71,782A. R.A. Campbell, G.L. Kurtz,* F. Bartos,* and D. Bartos.* Univ. of Oregon Health Sci. Ctr., Dept. of Pediatrics, Portland, Oregon.

DL-α-difluoromethylornithine (DFMO), a non-toxic irreversible inhibitor of ornithine decarboxylase, has been shown to block the increased synthesis of polyamines associated with cell proliferation in many tissues, including the thymus. DFMO blocks RNA, DNA and protein synthesis in lectin stimulated T-lymphocytes. Full thickness grafts of tail skin were exchanged between female C57B46 and BALB/C mice. These strains differ at the H-2 major histocompatability locus. Autografts were also placed in the same manner to monitor healing. Two percent DFMO drinking water was administrated ad libitum, intake was augmented by a single daily IP injection of 200 mg/Kg. The estimated total intake was 70 mg/mouse/d. Untreated allografts showed a mean onset of rejection at 7.4 d, followed by a typical pattern of acute rejection, with mean complete rejection at 13.0 d. All treated and untreated autografts showed normal healing characteristics. DFMO treated allografts had mean onset of rejection at 10.7 d and mean complete rejection at 16.2 d. The pattern of rejection in DFMO treated groups is more chronic in nature, swelling remains light, the hair is retained longer and the amount of tissue deterioration is significantly retarded. Complete rejection of DFMO treated allografts often appears to be associated with a loss of vascular flow from the graft bed. This is followed either by sloughing of the intact graft, or a gradual replacement of the graft with tissue of apparent host origin. Thus it appears that DFMO significantly retards rejection in this mouse allogenic skin graft model.

CYCLOSPORIN A IN CADAVER RENAL ALLOGRAFTS. B.J. Carpenter,* N.L. Tilney,* T.B. Strom, M.R.Garovoy, J.M.Lazarus. Departments of Surgery and Medicine, Brigham and Women's Hospital, Boston, MA

Our experience using Cyclosporin A (CyA) as the initial form of immunosuppression in 9 patients is reported. One dose of azathioprine (4mg/kg) was given intraoperatively. At 6 hours, CyA (17mg/kg) was started if urine output was greater than 40ml/hr. Despite intital diuresis, 5 patients became oliguric, requiring dialysis. Two others continued to diurese but had abnormal renal function (serum creatinine >5mg%). CyA doses were reduced to 8.5 - 12.5mg/kg if decreased renal function persisted for more than 5 days. Eight patients experienced at least one rejection episode while on CyA, 5 of these occurred within the first week. Rejection episodes were diagnosed clinically and substantiated by biopsies showing moderate cellular infiltrates. Seven of 8 initial rejection episodes were reversed by administration of steroids. Thrombocytopenia and leukopenia occurred in 7 patients, mild and transient in 6, life threatening in one patient who had been on azathioprine for 10 days after discontinuing CyA. This patient had the only serious infection - p. carinii pneumonia. No abnormalities of liver function were seen. Cellular and humoral immunity was depressed. Preliminary studies suggest some donor specific suppression of cellular immune response. At 3-10 months follow-up 4 patients have returned to dialysis. A fifth patient has a creatinine of 10.6mg%. Because of this initial poor experience withCyA, we now give low dose steroids earlier and on a continuous basis. Since then 3 of 4 grafts have good function. We find that CyA can be used in patients with poor renal function, does not eliminate early rejection and is enhanced by addition of low dose steroids.

● RECURRENT GLOMERULONEPHRITIS(GN) IN TRANSPLANTS. B.P. Croker,* M. Morzycka,* H.F. Seigler,* and C.C. Tisher. Duke Univ. Med. Center, Durham, N.C.

Clinical records and biopsy and nephrectomy specimens from 320 patients treated at Duke Univ. between 1965 and 1977 were examined to determine the type and incidence of recurrent GN in the allograft. A diagnosis of recurrent disease required that the histopathology of the transplant resemble the native kidney by light, immunofluorescence and electron microscopy. Of 204 patients with native and transplant tissue available for evaluation,57% or 117 had some form of chronic GN. Of the 117, there were 61 whose disease could be subclassified further. Idiopathic membranous GN was documented in 7, IgA nephropathy in 5, focal glomerular sclerosis in 20, type 1 membranoproliferative GN in 16, type 2 membranoproliferative GN in 2, proliferative GN in 9, and anti-GBM disease in 2. In this group of 61, there were 19 patients with 21 grafts in which there was evidence of recurrent GN including 4 each with idiopathic membranous GN and focal glomerular sclerosis, 7 with type 1 membranoproliferative GN, 2 each with type 2 membranoproliferative GN and anti-GBM disease, and 1 each with IgA nephropathy and proliferative GN. There were 104 living related donor kidneys grafted into patients with chronic GN, and 78 had tissue available for evaluation. In this group there were 15 patients with 16 grafts with recurrent GN. There were 55 cadaveric donor kidneys transplanted into patients with chronic GN, and 39 had tissue available for evaluation. In this group there were 5 examples of recurrent GN. Thus, recurrent GN can occur in a variety of histologic subtypes and, in this study population, recurrent GN was more common in grafts from living related donors.

● THE SONOGRAPHIC EVALUATION OF THE TRANSPLANTED KIDNEY: A PROSPECTIVE STUDY. C. Cruz, H. Hricak, M. Uniewski, W.R. Eyler, N.W. Levin. Henry Ford Hospital, Detroit, Michigan.

Serial sonograms were performed prospectively on 36 transplant recipients, beginning 48 to 72 hours after surgery, and serially weekly for 2 months, or until discontinuation of immunosuppression. Using criteria derived from our previous retrospective experimental and clinical observations (Radiology 133: 443-7, 1979) sonograms were interpreted without knowledge of clinical, laboratory or histological findings, and only then were correlated with these. Diagnosis of rejection was confirmed by nephrectomy (N=5) and biopsy (N=4). Diagnosis of ATN (N=8) was confirmed by response to conservative management that excluded treatment for acute rejection. Well-functioning kidneys (N=22) always displayed normal renal architecture and an increase in volume (18%,24%,29% at the end of 2,4, and 8 weeks respectively). During the course of ATN, normal sonographic features and growth rate were maintained. During acute rejection episodes (N=19), the following abnormalities were seen: 1) sudden increase in volume (84%), 2) prominent medullary pyramids (79%), 3) decreased amplitude of renal sinus echoes (74%), 4) abnormal echogenicity (68%). An absolute correlation was found between clinical rejection and sonographic deterioration from baseline. Lymphoceles were detected in 15 patients, 4 requiring aspiration, 5 associated with rejection episodes which reversed with antirejection therapy and 6 clinically insignificant. Using baseline studies and appropriate criteria, sonography is sensitive and specific in the diagnosis of clinically significant acute renal allograft rejection.

● ADVANTAGE OF LONG TERM ALTERNATE DAY STEROID THERAPY IN RENAL TRANSPLANTATION: A CONTROLLED STUDY Francis Dumler, Nathan W. Levin, Gabriel Szego,* Nina Vulpetti,* and Luther E. Preuss,* Henry Ford Hospital, Detroit, Michigan.

The long term effectiveness of alternate day steroid therapy in renal transplantation is not well documented. We report a 57 ± 27 month experience in 76 patients: cadaver (CA; n=23) and living related (LA; n=15) recipients on alternate day steroids, and cadaver recipients on daily steroids (CD; n=38). Mean prednisolone dosages were 18 ± 3 mg qod, 17 ± 3mg qod and 13 ± 3mg qd respectively. There were no differences between groups in serum creatinine (CA: 1.4 ± 0.6; LA: 1.5 ± 0.6; and CD 1.8 ± 1.6 mg/dl) or creatinine clearance (CD: 79 ± 19; LA: 70 ± 24; CD: 67 ± 27 ml/min). The incidence of chronic rejection was greater in CD than CA (28% vs 14% $p<.01$) but acute rejection episodes (3.1 vs 2.9 episodes per one thousand patient months; p=ns) were similar in both groups. The prevalence of obesity, hypertension, hyperglycemia, hypercholesterolemia and hypertriglyceridemia was similar in all groups, and there were no differences in serum calcium, alkaline phosphatase or PTH concentrations. The incidence of radiological osteopenia and subperiosteal erosions was similar in all groups. The frequency of femoral head osteonecrosis (ON) was significantly greater ($p<.05$) in CD (16%) than in CA (3%) and LA (0%). CA patients had a lower frequency of infectious episodes than CD patients (.192 vs 1.42 episodes per one thousand patient months; ($p<.01$). Alternate day steroid therapy effectively maintains graft function in renal transplant patients, decreases the incidence of ON and reduces the frequency of infectious complications.

RELATED RENAL TRANSPLANTATION IN POORLY-MATCHED DIABETIC RECIPIENTS AFTER DONOR-SPECIFIC TRANSFUSIONS. N.J.Feduska‡ F.Vincenti, W.Amend, Y.Iwaki‡ G. Opelz‡ P. Terasaki‡ R. Duca‡ S. Hopper‡ and O. Salvatierra‡ U. of California, San Francisco and U. of California at Los Angeles.

In our center a new method has been developed and applied to renal transplantation in insulin-dependent diabetic recipients (IDDRs). Donor-specific transfusions (DSTs) have been given according to a uniform protocol prior to poorly-matched (high MLC: S.I.≥ 7) primary related transplants (RTs) in an effort to improve graft survival (GS). Poor matches formerly eliminated the possibility of such RTs. According to this protocol RTs were performed if serial immunologic monitoring detected no specific evidence of recipient sensitization consequent to the DSTs. During the past 2 yrs. 11 RTs with high MLC and DSTs have been performed for IDDRs; only one has been rejected (in a patient who intentionally terminated immunosuppression.) GS for this group is 89%/89% at 1/2 yrs., respectively. The quality of renal function has been excellent with a mean serum creatinine of 1.6/1.8 mgm/dcl at 1/3 mos. (with the highest at present 2.6 mgm/dcl) GS for 7 RTs in IDDRs with low MLC (S.I.<7) and no DSTs was 100%/100% at 1/2 yrs., but for 9 RTs in IDDRs with high MLC and no DSTs was 44%/44% at 1/2 yrs. GS for 71 primary cadaver transplants (CTs) in IDDRs was 34%/28% at 1/2 yrs. DSTs make excellent results possible for RTs in IDDRs, even when the donors are poorly matched by MLC testing. This new method results in better GS than has been achieved with CTs or RTs with high MLC and no DSTs.

CONTROLLED RE-ASSESSMENT OF THE USE OF ANTITHYMOCYTE GLOBULIN (ATG) TO PREVENT REJECTION OF CADAVERIC RENAL ALLOGRAFTS (CTX). P. Gailiunas, J. H.Helderman, C. Atkins*, P. Peters, and A. Hull. Univ. of Texas, SWMS, Dallas, Texas.

Controversy over the value of ATG in prevention of renal transplant rejection continues. We therefore undertook a controlled study of equine ATG (Upjohn, ATGAM) in consecutive CTX recipients from 10/77 - 9/79. 36 subjects received ATG 15 mg/kg IV daily for 14 days then on alternate days for an additional 14 days. Peripheral T cell counts were made by the E rosette technique but doses were not adjusted by the measurement. 29 pts received the full 21 doses of ATG while the drug was stopped for sepsis (4), thrombocytopenia (1) and severe constitutional symptoms (2). 43 subjects received only our standard immunosuppression regimen of prednisolone and azathioprine. ATG clearly delayed the onset of the first rejection. In only 4/36 (11%) patients did the 1st rejection occur in the first 2 wks compared to 23/43 (53%)for controls. No control escaped at least one rejection episode. While ATG treated pts experienced 9 1st rejections between 1 and 3 mos postop and 8 such episodes after 3 mos. The one year graft survival rate for ATG treated patients (56%) was somewhat better than control (41%), $p < 0.1$. There was a significant and late loss in the ATG group so that 1.5 yr and 2 yr graft survival rates were nearly identical to control. Mortality rates at 2.5 yr were the same (5/36, ATG and 6/43, control), although the ATG group experienced a series of unusual gastrointestinal and infectious complications. We conclude that equine ATG given in this fashion delays but does not prevent a rejection. This delay in rejection did not result in a reduction in mortality or morbidity.

PROXIMAL TUBULAR (PT) DYSFUNCTION IN A DIABETIC (D) TRANSPLANT RECIPIENT MANIFESTED BY INSULINURIA. Peter Fisher,*John M. Barry, Douglas J. Norman, and William M. Bennett (intr. by James Walker). Univ. of Oregon Hlth. Sci. Ctr., Divs. of Nephrol. and Urol., Portland, Oregon.

Although PT functional abnormalities are common with successful transplants, the inability to properly metabolize insulin (In) has not been reported. A 26 year old woman with end-stage D nephropathy received an HLA-identical kidney from a sibling donor. Massive urine output averaging >2L/hour began immediately. During intravenous constant infusion of pure pork regular In, urine and plasma (P) immunoreactive In levels were simultaneously determined by radioimmunoassay. Hourly urine volume (UV), the amount of infused In per hour (U/hr) and blood sugar were recorded.

DAY:	1	2	3			4		
Infused In U/hr	10	12	5	5	5	4	4	4
P In μIU/ml*	794	755	487	577	475	505	492	444
Urine In μIU/ml	240	384	87	78	35	42	19	25
UV ml/hr.	2600	1200	2300	850	475	900	250	650
Blood sugar	325	872	400	225	75	400	175	75

*Urine In pre- and post-In infusions <10 μIU/ml.

Although the rate of In infusion was decreased over the four days, plasma In remained high. As normal filtration rate continued, urinary In fell progressively, reflecting increased tubular catabolism.

We conclude: 1) transplanted kidneys may exhibit PT dysfunction resulting in insulinuria; 2) renal loss of exogenous In may contribute to the high In requirements of diabetic subjects undergoing living, related donor transplant and massive early diuresis.

● COMPARISON OF THE BIOAVAILABILITY OF ORAL PREDNISONE AND PREDNISOLONE IN KIDNEY TRANSPLANT PATIENTS. J.Gambertoglio, F.Frey‡ J.Birnbaum‡ W.Amend, Univ. of Calif., San Francisco CA.

Kidney transplant patients are usually administered prednisone (p), rather than prednisolone (po) for immunosuppressive therapy. However, p requires reduction to po in order to be pharmacologically active. Seven stable kidney transplant patients were studied at least 1 yr. post transplantation and had good kidney function(SCr 0.9-2.1mg%). Liver function and serum albumin were normal. On separate occasions, each received their usual oral dose of p (12.5-22.5mg), an equivalent oral dose of po, and an equivalent IV dose of po. Plasma po levels were determined by HPLC. After oral p, peak plasma po levels occurred from 0.5-2.0 hrs. and ranged from 212-508 ng/ml. Similar values were obtained after oral po with peak levels ranging from 237-556 ng/ml at 0.5-3.0 hrs. Most important, the systemic availability of po from oral p and oral po was not significantly different relative to IV po, being 86.7± 6.4% and 91.9±5.8%, respectively. Thus both oral preparations tested, p and po, provide the same availability of po and conversion of p to po appears unimpaired. Kidney transplant patients should obtain the same effect and be able to receive either oral corticosteroid.

● LYMPHOCYTE SUBPOPULATIONS IN HUMAN RENAL TRANSPLANTATION ANALYZED BY FLOW CYTOMETRY.
R.D. Guttmann, R.Poulsen*, Transplantation Serv. & Dept. Path., Royal Victoria Hosp. & McGill Univ., Montréal, Québec.

A longitudinal study of surface markers on peripheral blood lymphocytes from uremic patients prior to and serially following renal transplantation have characterized subpopulations using a Fluorescence Activated Cell Sorter (FACS). Data has been obtained on cells isolated immediately before and after transplantation, prior to and during rejection crises, during periods of stable normal allograft function, during infection, and following allograft nephrectomy such that post-transplant study and risk periods compared are similar for the group regardless of outcome. For each cell studied, light scatter profiles (size) and cell surface antigen array have been characterized by fluorescent antibody reagents to 1) surface IgM & IgG, 2) Ia and 3) T lymphocyte subsets using monoclonal antibodies (Ortho). A dynamic situation occurs post-transplant with significant "blast" cell presence, particularly marked before and during rejection associated with increased numbers of helper/inducer cells. Large, but not small lymphocytes with the cytotoxic/suppressor marker are also associated with rejection. Of particular note, is that a large subpopulation of Ia+ T & B cells, emerges following alloimmunization and prior to rejection and may be present in patients with stable function between 30-60 days. The FACS approach allows acquisition of quantitative data and identification of relevant subpopulations for sorting.

● THE PRE-TRANSPLANT CELL MEDIATED LYMPHOLYSIS ASSAY (CML) IS PREDICTIVE OF ACUTE REJECTION EPISODES (ARE) AND LONG-TERM GRAFT FUNCTION AND SURVIVAL IN RENAL TRANSPLANTATION. W.E. Harmon, P. Lavin*, J.R. Ingelfinger, R.H. Levey*, W.E. Grupe, R. Parkman*, Harvard Medical School, Boston, Mass.

The CML is an in vitro assay of the ability of recipient lymphocytes to generate specific cytotoxicity against a prospective donor's histocompatability antigens. To determine whether the CML can be correlated with renal transplant (Tx) outcome, we prospectively studied 24 living related Tx performed during the past 3 years. Of the 11 patients with low CML (absolute cytotoxicity<5%) only one had an ARE. In contrast 8 of 13 patients with high CML had ARE ($p<0.05$). In addition time to graft dysfunction (Cr>1.5) was shorter in patients with high CML ($p=0.006$) and 3-year graft survival was lower ($p=0.05$). To compare the significance of a high CML with that of a positive mixed lymphocyte culture (MLC) we used a logistic model of probability of ARE. Both CML and MLC were equally prognostic for the occurrence of ARE ($p=0.08$). More importantly the combination of CML and MLC added 40% to the accuracy of prediction of ARE as measured by the log-likelihood function associated with the underlying linear logistic model. That ARE was predictive of long-term graft outcome was demonstrated in a retrospective analysis of 125 living related and cadaver Tx: at least one ARE within 2 months of Tx was correlated with both time to graft dysfunction ($p<0.0001$) and 5-year graft survival ($p=0.003$) Therefore, the combination of CML and MLC was a superior predictor of ARE and, consequently, of long-term graft outcome. We conclude that CML should be considered an integral part of the immunological evaluation of potential living related donor-recipient pairs.

UTILITY OF BETA-2-MICROGLOBULIN MONITORING AFTER RENAL TRANSPLANTATION. L. Lee Hamm* and J. H. Helderman, P. Gailiunas, L. Edwards*, P. Peters, and A. Hull. U of Tx, SWMS, Dallas, Tx.

The diagnosis of rejection after renal transplantation remains difficult with frequent resort to subjective criteria. An objective, reliable indicator of early rejection is unavailable. Monitoring serum and urine beta-2-microglobulin (B-2-M) by a commercially available radioimmunoassay (Phadebas) is reported to be such an indicator; B-2-M is a low molecular weight protein which is filtered and then reabsorbed and catabolized proximally. Serum and urine B-2-M were assessed in 20 consecutive transplant recipients with complete data available for 20 rejections in 17 pts. Elevations in serum B-2-M and in serum: urine B-2-M ratios (S:U) were frequent on the days before the diagnosis of rejection and often preceeded elevations of serum creatinine. Serum B-2-M rose in 11/16 episodes 1 day and 9/15 episodes 2 days prior to the diagnosis of rejection while the S:U rose in 10/14 and 6/12 on these days. The correlative function, however, was not as consistent as hoped. In the 15 episodes in which creatinine rose on the day of diagnosis of rejection, B-2-M rose in only 8 and S:U in only 7. During post-transplant ATN, serum B-2-M showed a general downward pattern but with frequent isolated and unexplained elevations. We conclude that monitoring of serum B-2-M and S:U is an objective but adjunctive means to detect early rejection and can support the diagnosis of ATN. But the variability of values in practice makes interpretation of any single measurement dangerous. If B-2-M is to be used clinically, a pattern derived from frequent measurements needs to be obtained.

● THE ROLE OF LECTIN ACTIVATED SPLENIC SUPPRESSOR CELLS (SC) IN THE GENERATION AND MAINTENANCE OF TRANSPLANT IMMUNITY. J.H. Helderman, D. Ludwin*, P. Gailiunas. U of Tx, SWMS, Dallas, Texas.

The generation of splenic SC has been implicated as a mechanism of active enhancement of organ allografts. We therefore studied the impact of lectin activated SC on the generation of and the functional integrity of sensitized effector cells. Dose-response studies in rat spleen revealed maximum suppression of DNA synthesis (98%) at 50 µg/ml PHA, a concentration which gave a maximum DNA synthetic response in thymus (49 fold) and lymph node (42 fold). The SC was found in the nylon wool adherent splenic population (A) and was removed by treating with anti T cell sera. That the suppression was caused by SC was demonstrated by mixing the lectin treated A after careful wash with freshly treated normally responsive lymph node. There was a progressive fall in DNA synthesis as the fraction of A was increased. We next tested the capacity of the lectin activated A to prevent the development of alloimmunity in the mixed lymphocyte culture. In 3 party experiments these putative SC suppressed both the blastic response (uptake of 3H-tdr) and the generation of cytotoxic T cells (CT) by ^{51}Cr release. When the SC were pre-incubated with sensitized CT for 20 min prior to presentation of the appropriate target cell, killing was also diminished. Sensitized Lewis CT against Buffalo gave 18% specific chromium release which was reduced to 7% by pretreatment with PHA treated A, a diminution of 61%. Lectin activated SC thus inhibit 1) the alloimmune proliferative response, 2) generation of CT, and 3) CT effector activity. These effects suggest an important role for SC in active immune enhancement

SIGNIFICANCE OF LYMPHOCYTURIA IN RENAL ALLOGRAFT REJECTION. G.G. Krishna, S.K. Fellner, Division of Nephrology, Department of Medicine Emory University School of Medicine, Atlanta, Georgia

Definitive diagnosis of acute rejection may be difficult in the immediate post transplant period, particularly in the setting of acute tubular necrosis with oliguria. Lymphocyturia was looked for daily in 60 patients following transplantation with the use of a simple staining technique with methylene blue. Thirty-seven acute rejection episodes associated with deterioration in renal function were observed. Other causes of decreased renal function such as vascular occlusion, urologic obstruction or infection were carefully excluded. Thirty-four (92%) of the 37 acute rejection episodes were accompanied by significant lymphocyturia (3 small lymphocytes/HPF or at least 3 to 5 large lymphocytes per slide).

Lymphocyturia was recognized concommitant with the rise in serum creatinine in 20 of the 34; whereas, in 14 it preceded the rise in serum creatinine by an average period of 3.5 days. Twenty-four (71%) of these 34 rejection episodes were reversed by high dose steroid administration, and only 2 of them showed persistent lymphocyturia following treatment. On the other hand, 9 of the 10 non-responders to steroid therapy showed persistent lymphocyturia, 8 of them eventually undergoing transplant nephrectomies.

Detection of lymphocyturia not only is of value in the diagnosis of acute allograft rejection, but also is useful in determining the prognosis of allograft survival in immediate post-transplant period.

PREVALENCE OF SERUM ANTIBODIES TO LEGIONELLA PNEUMOPHILA AND PITTSBURGH PNEUMONIA AGENT IN RENAL TRANSPLANT RECIPIENTS. Patricia Lyons*and Sheila Moriber Katz, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

Legionella pneumophila (LP) and Pittsburgh Pneumonia Agent (PPA) are two recently identified bacteria that produce pneumonia in debilitated patients. Infection by LP is reported in patients undergoing renal transplantation (Bock, et al, Lancet 1:410-413, 1978), and PPA was originally isolated from renal transplant recipients (Pasculle, et al, Lancet 2:58-61, 1979). Therefore, we studied the prevalence of serum antibodies to LP (serogroups I-VI) and PPA in 51 adults with renal allografts of greater than 6 months duration. 72 healthy adults were the control group. To measure antibodies to either LP or PPA, a single serum sample was tested by the conventional indirect immunofluorescence test, using appropriate positive and negative control sera. By this method, a titer of $\geq$1:256 to LP is presumptive of past infection by LP. None of 51 patients had a titer of $\geq$1:256 to LP. Two of 51 (3.9%) had 1:128 to LP; 3 of 51 (5.9%) had 1:64 to LP. Only 1 of 5 patients with titers $\geq$1:64 to LP had prior history of pneumonia, but that was staphylococcal, proven by culture. None of 51 renal transplant recipients had titers $\geq$1:64 to PPA. In the control group, none of 72 persons had a titer of $\geq$1:256 to LP; 1 of 72 (1.3%) had 1:128 to LP; 2 of 72 (2.7%) had 1:64 to LP. Moreover, none of 72 had a titer of $\geq$1:64 to PPA. There is no difference in prevalence of antibodies to LP and PPA between the control and test groups. The data presented herein suggests that our population of renal transplant recipients is not prone to infection by either LP or PPA.

POST-TRANSPLANT (Tx) HYPERPARATHYROIDISM (HPTH): THE PATHOLOGIC ANATOMY. Barbara Lenfesty,* Mark Vetto,* John M. Barry, and David A. McCarron. Univ. of Oregon Hlth. Sci. Ctr., Depts. Med. and Gen. Surg., Portland, Oregon.

Persistent HPTH that emerges following successful kidney Tx represents the legacy of diffuse parathyroid hyperplasia that develops with chronic renal failure. As such, Tx-HPTH is considered to be distinct from adenomatous (primary) HPTH in terms of multiple gland involvement. To assess the pathologic anatomy of Tx-HPTH, we measured individual and total gland volume at the time of total parathyroidectomy and forearm reimplantation in 14 successful (mean serum creatinine 1.3 mg/dl) Tx recipients with persistent HPTH (mean time after Tx 40.8 mo).

Mean ± S.E.	Left Superior	Right Superior	Left Inferior	Right Inferior
Volume cm^3	0.46 ±0.08	0.80 ±0.24	0.63 ±0.11	1.01 ±0.21
% of Total Volume	16.3 ± 2.6	24.5 ± 4.4	24.2 ± 4.0	34.4 ± 4.5

Mean total parathyroid volume was 2.94 cm^3. By ANOVA statistics, the hyperplasia of right inferior parathyroid gland was greater ($p<.02$) than that of the other glands, while the left superior gland was smaller ($p<.05$) than the other glands. Inferior glands hypertrophied more ($p<.025$) than the superiors and right-sided glands were more enlarged than the left ($p<.001$).

We conclude: 1) that gland enlargement in TX-HPTH is non-homeogeneous, 2) in contrast to normal anatomy, the inferior glands predominate in size, 3) similar to reports in primary HPTH, one gland (right inferior) is likely to be more hypertrophied in Tx-HPTH.

INCIDENCE & SIGNIFICANCE OF RECURRENT FSGS IN RENAL ALLOGRAFTS. S. Maizel*, R. Sibley, J. Horstman,* C.M. Kjellstrand, R.L. Simmons. Univ. of Minnesota Hosp Depts. Surg., Path. & Med., Minneapolis, MN

The significance and incidence of recurrent focal segmental glomerulosclerosis/hylanosis (FSGS) in renal allografts remains unclear. Case reports, uncontrolled multicenter studies and failure to distinguish recurrent FSGS from chronic rejection have all contributed to the confusion. To resolve this we reviewed all patients undergoing renal transplantation at a single center in the last 13 yrs in whom native renal tissue was available to confirm FSGS. All allograft tissue subsequently obtained was then reviewed by a single pathologist without knowledge of the clinical course. Three distinct histological groups of native kidney lesions were identified: 1) only FSGS; 2) FSGS + focal segmental mesangial proliferation (MP); 3) MP, either diffuse or focal, who subsequently developed FSGS. Graft survival, incidence of recurrent FSGS distinct from changes of rejection and long term outcome was significantly different between the groups and controls (grp 4). Recurrence was present histologically in 5 (3cad, 2 LRD) of 34 kidneys (18%) but caused graft loss in only one.

Grp	#pts	# Tx	Graft Survival 12 mo	Graft Survival 48 mo	Incidence of Recurrence # Tx	Incidence of Recurrence %
1	18	22	70%	70%	1	4.5%
2	6	8	87%	57%	2	25%
3	4	4	50%	25%	2	50%
4	63	84	73%	65%	---	---

It is clear that FSGS alone recurs infrequently and rarely causes graft loss but when found with MP in native kidneys it does frequently recur and may be associated with significant proteinuria and early graft loss.

RENAL TRANSPLANTATION IN ALPORT'S SYNDROME. DEVELOPMENT OF ANTI-GBM GLOMERULONEPHRITIS. Dawn Milliner*, Keith Holley, Alkis Pierides, Division of Nephrology and Department of Anatomic Pathology, Mayo Clinic, Rochester, Minnesota.

Anti-GBM glomerulonephritis has been reported in the transplanted kidney of patients with Alport's syndrome. It has been suggested that the basement membrane (BM) of these patients lacks an antigen(s) common to normal BM and that this accounts for the development of anti-GBM antibodies against the allograft.

10 patients with Alport's syndrome, aged 17-50, have been transplanted at this institution during the past 14 years. The mean followup is 68.5 months (range 5-162). All 10 are currently well. 3 patients lost their first allograft but 2 were successfully retransplanted. One patient returned to dialysis.

Of the 9 successfully transplanted patients, 8 have serum creatinine levels < 2 mgm/dl, but only 2 have a normal urinalysis. 7 have stable non-nephrotic proteinuria and intermittent microscopic hematuria. Histology of the 3 lost allografts showed changes of acute rejection in 1 and in 2 allografts a diffuse crescentic proliferative glomerulonephritis with a strong GBM linear IgG pattern on IF. Circulating anti-GBM antibodies were present in 1 of these patients. Both patients with crescentic lesions have received a second transplant and renal function remains excellent 1 and 4 years later, although recurrence of circulating anti-GBM antibodies was found in one.

These results indicate that post-transplant survival and renal function in patients with Alport's syndrome can be very good, despite the occasional occurrence of anti-GBM GN.

REGIONAL KIDNEY SHARING PROGRAM FOR HIGHLY SENSITIZED PATIENTS. Douglas J. Norman, Andrew S. Goldstein,* and John M. Barry. University of Oregon Health Sciences Center (UOHSC), Transplantation Service, Portland, Oregon.

The probability that patients with antibodies to many HLA antigens can ever be transplanted is low. Results from the most recent international transplantation study, however, indicate that the degree of sensitization does not bear on graft survival if a negative donor-specific crossmatch is obtained. Indeed, many of these patients have received multiple transfusions, which predicts a good prognosis. The problem is that the pool of kidneys available to them is severely limited.

In order to increase the pool of kidneys available to highly sensitized patients awaiting cadaver kidney transplantation, members of the Western Association of Transplant Surgeons (WATS) began a serum exchange and kidney sharing program in the Fall of 1978. Briefly, sera from highly sensitized patients are sent to the UOHSC Histocompatibility Lab each month from all participating centers. WATS trays are made containing the most recent and most reactive sera of all patients and sent to each participating center. Each time a member laboratory performs a crossmatch on a locally retrieved kidney, a WATS tray containing sera of all sensitized patients in the region is included. Since 1978, four highly sensitized patients have been transplanted as a result of a negative crossmatch on the WATS tray. Three of the four have functioning grafts at 8, 13 and 21 months. This program, along with those of SEOPF and SONY, can serve as a model for other regions who wish to increase the pool of kidneys available to highly sensitized patients.

SERUM B_2 MICROGLOBULIN(B_2): A MARKER FOR TRANSPLANT REJECTION(TR) IN LIVE-RELATED DONOR TRANSPLANTS. G Morrison, J Nally, P Kimmel, R Grossman, L Perloff, C Barker. Univ of PA, Phila, PA

This study was undertaken to evaluate if serum levels and/or urinary excretion of B_2, a small molecular weight protein(filtered by the glomerulus and reabsorbed by the proximal tubular cell)were sensitive markers for TR. Serum and 24 hr urine for creatinine(cr) and B_2 were collected daily to determine clearances of creatinine(Ccr)and B_2(CB_2), fractional excretion of B_2(CB_2/Ccr)and urinary ratio ug B_2/gm cr. Sixteen patients(6F/10M)with a mean age±SD of 28±10 were followed daily, after receiving a live-related kidney transplant, for clinical signs of TR. Ten of 16 patients who had a fall in serum cr(Scr) to ≤2.0 mg/dl after transplantation had a total of 13 episodes of TR defined as a Scr rise of ≥0.5 mg/dl with one or more of the following: T°≥100°C, BP≥150/90, decreasing urine output and tender graft. (PR) and (R)denote results prior to rejection and at initiation of TR treatment respectively. Results were analyzed retrospectively and expressed as mean±SD.

	nl range	PR	R	p
Scr(mg/dl)	≤2.0	1.3±0.4	2.3±0.8	<.005
GFR(ml/min)	≥ 80	74±23	37±19	<.005
SB_2(mg/L)	≤2.4	2.3±0.3	5.9±1.6	<.005
CB_2/Ccrx100(%)	≤.05	2.3±.02	1.5±.02	NS
ug B_2/gm cr	≤200	3758±4129	4864 5895	NS

In summary: 1) urinary B_2 excretion was variable and did not correlate with falling GFR & rising Scr: 2) rising SB_2 during rejection correlated with falling GFR & rising Scr: 3) SB_2 appears to be a sensitive marker for decreasing GFR and early TR.

INFLUENCE OF HLA-HAPLOIDENTITY ON THE SURVIVAL OF RENAL GRAFTS FROM LIVING RELATED DONORS. M.Papadimitriou,* Z. Polymenides,* G. Sakellariou,* A. Dimitriadis,* and P. Metaxas,*(intr. by N.S.Bricker). 2nd Propedeutic Department of Medicine, Aristotelian University, Thessaloniki, Greece.

Fifty-six kidney transplants from haplogenotyped live donors (parent or sibling) were analysed for survival and degree of function. Three groups of donor-recipient pairs were studied. The first consisted of 16 pairs sharing one of the most frequent linkage disequilibrium antigen combinations encountered in the Greek population (A_1B_8, A_2B_{12}, A_3B_7, $A_{11}B_5$, $A_{11}BW_{35}$ and AgB_{12}). The second group consisted of 16 pairs differing in one of the above haplotypes. The third group consisted of 24 pairs with 2 other antigen matches. Cases with more than 2 antigen matches were excluded. Immunosuppression was standard in all patients. No graft was lost in the first group, 10 out of 16 grafts were lost in the second group, and 7 out of 24 were lost in the third group. The mean survival time (±SE) in the 1st group was 63 ±9.9 months, in the 2nd group 37 ±8.0 months and in the third 42 ±4.3 months. Statistical analysis showed significant differences between the 1st and 2nd groups (t=3.18, p<0.005) and the 1st and 3rd groups(t=2.88, p<0.01). Finally, the mean serum creatinine (±SE) (in mg/100 ml) was 1.33±0.10 (16 cases), 1.71±0.14 (6 cases) and 1.95 ±0.08 (17 cases) in the 3 groups respectively.There was a statistically significant difference between the 1st and 2nd groups (t=3.36,p<0.005) and the 1st and third group (t=6.8, p<0.001). It is concluded that the selection of a haplogenotyped related donor sharing one of the above antigen combinations with the recipient provides better survival of the graft. This could imply that in this situation MLC determinants are shared by donor and recipient

RECURRENCE OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS IN CHILDREN FOLLOWING RENAL TRANSPLANTATION.
Z.L. Papadopoulou, G.B. Helfrich*, M.E. Turner*, S. Shahinfar,* C.B. Currier* and P.L. Calcagno, Georgetown Univ. Med. Ctr. and Washington Hosp.Ctr. Washington, D.C.

Focal segmental glomerulosclerosis (FSGS) is a frequent cause of chronic renal failure and it has been reported to recur at an alarmingly high frequency in adults following Kidney transplantation. The frequency of recurrence in children is not well known. 12 children with FSGS received a total of 10 living related(LR)and 5 cadaver(Cd)allografts since 1975. Patient ages ranged between 2.2 to 16.0 yrs. at time of the first transplant. Nehprectomy of the host kidneys was performed in all children. Of the 9/12 pts. who received 10 LR allografts, 8 pts have a functioning first graft at 1.4 to 5.0 yrs(mean 3.7 yrs)with no evidence of proteinuria and/or recurrence of FSGS. In 1 pt.,a recipient of an HLA-identical kidney,heavy proteinuria developed at 6 days post-transplant,and histopathologic changes typical of FSGS were documented at 120-days biopsy and at graft nephrectomy one year later.FSGS recurred in the same child at 7 days following a second HLA-identical renal allograft.Of the 3/12 children who received 5 Cd renal allografts, 1 pt. has a normal functioning first graft at 4.8 yrs. with no evidence of recurrence of FSGS.The other 2 pts.have undergone a total of 4 graft rejections with no evidence of recurrence of disease.In conclusion,FSGS recurred in 1/12 children(8%)or in 2/15 renal allografts(13%).9/12 children(75%)with normal functioning first grafts, have no evidence of recurrence of FSGS at 1.4 to 5.0 yrs. (mean 3.8 yrs.) post-transplant.

B-2 MICROGLOBULIN(B-2): A SENSITIVE GUIDE TO RENAL DYSFUNCTION IN TRANSPLANT RECIPIENTS.
D.M.Roxe, S.Santhanam, F.Siddiqui, F.del Greco & J.Wolf. N'western Univ Med Sch, Nephrology/Hypertension,Dept Med & Div.Transplantation, Dept Surg,Chi, Ill.

Serum and Urine samples from 47 transplant recipients were analyzed for B-2 for 21 days after transplantation to find possible acute rejection(AR)episodes. Because early AR causes glomerulotubular imbalance our criteria were 1)Serum B-2 rise by 20% or more from the previous day 2)urine B-2 fall & 3)serum/urine B-2 rise by 70% or more from the previous day, thus isolating events with a fall in GFR and a rise in extraction of B-2 from luminal fluid. Criteria were met 40 times in 47 patients at risk for 987 days. In positive cases mean rise in serum B-2 was 66%, fall in urine was 50%, and rise in ratio was 515%. Serum creatinine rose by a mean of 70.3% within 5 days of +B-2 criteria. 21 episodes were not diagnosed as AR by clinicians using classic clinical criteria. In 11 of these serum creatinine rose, in 6 others clinical diagnosis was acute renal failure, 3 had possible renal artery stenosis, 1 had daily dialysis precluding evaluation of creatinine. We conclude that 1)B-2 criteria gave a useful guide to transplant dysfunction and may be a more sensitive index of AR than present methods. 2)B-2 may be used from day to day when dialysis alters creatinine. 3) Simultaneous serum and urine determinations are needed to use B-2 for AR.

● INTRAFAMILIAL RENAL TRANSPLANTATION: LONG TERM SURVIVAL RATES AND RISK FACTORS.
R.R.Riggio, M.Suthanthiran, J.Cheigh, W.Stubenbord*,J.Sullivan,L.Tapia, J.Chami*,S.Saal*,M.Fotino*,K.H.Stenzel,and A.Rubin. Rogosin Kidney Center,The New York Hospital-Cornell Medical Center, New York, New York.

The role of multiple "risk" factors thought to affect patient and graft survival was analyzed in 231 recipients of a related donor allograft. The survival rate at 1 year for all transplant recipients was 88%;it increases to 93% and 100% for those transplanted since 1973 and 1976, respectively. The cumulative survival rate (CSR) of two haplotype-matched grafts was 82 ± 5% and 60 ± 10% at 1 and 10 years following transplantation, respectively. The CSR of one haplotype-matched grafts was 60 ± 4% and 34 ± 4% for the same periods. MLC indices clearly identified haplotype differences but were unpredictive of ultime graft outcome in 51 one haplotype-matched recipients. Complement dependent cytotoxic antibody screening (CDC) was equally unpredictive; the CSR in sensitized recipients (> 5% CDC) at 1 year was 63% compared to a value of 60% for those not sensitized. Pretransplant blood transfusions had no discernible affect on the CSR of grafts with either degree of matching. Native kidney disease, with the exception of diabetes, had no measurable effect on either patient or graft survival through the first year of transplantation. Pretransplant dialysis therapy did not influence graft outcome but was associated with higher patient survival in recipients receiving one haplotype-matched grafts. We conclude that haplotype-matching remains the dominant factor in the selection of related donors; MLC, blood transfusions and sensitization status contribute little, if anything, to the ultimate outcome.

ANTI-REJECTION THERAPY(Rx)IN PEDIATRIC RENAL TRANSPLANTATION,
Reid Selden*, Jeffrey Friedman, & Matthew Kaplan,N.Y. Hosp.Cornell Univ. Med. Coll,N.Y.,N.Y.

The outcome of Rx was evaluated retrospectively in 72 transplants done in 58 patients(Pts) who had been followed for > 1 year. 271 pulses(P_1) of Solumedrol 5mg/kg IV q12h x 6, 17 double dose pulses (P_2) of Solumedrol 10mg/kg IV q12h x 6 given after unsuccessful P_1 and 29 single pulses(SP_1) to outpts.were given. Rejection was defined using 3 criteria:graft tenderness and/or enlargement(G),fever (T),and a rising creatinine(Cr).Response(R) was defined as complete resolution of G or T or improvement of Cr. Incidence and R data for all pts. receiving P_1 by presenting criteria follows:

	G	T	Cr	G+T	G+Cr	T+Cr	G+T+Cr
Incidence(%)	3	17	37	6.5	5	23	8.5
Response(%)	83	89	75	83	64	67	48

Cr +any other sign predicted poorer outcome. T alone and T+G correlated with R($p<.02$).P_1 Rx during the first 6 months post transplant had a better R than later P_1's($p<.05$). Number of rejections and time after transplant of the last rejection had no correlation with graft survival.Pts. treated with P_1 and P_2 had similar R's(73% vs 65%). Pts. given SP_1 Rx had poorer R(41%, $p<.01$). SP's given 6 months post transplant had a better R than those given later($p<.05$). Complications of Rx included sepsis (3),pneumonia(6), GI bleed(3), hypertension(23) with encephalopathy(5). Encephalopathy was not related to number of pulses,pulse dose or time of Rx after transplant.No graft loss or death was related to Rx. Pulse steroid therapy is an effective and safe means of treating acute transplant rejection. Higher dose repeat Rx should be considered when initial Rx fails. Children may be more responsive and have fewer side effects than adults receiving similar therapy.

THE RELATED DONOR: LONG-TERM EFFECTS, Roberta G. Simmons,* & Linda Kamstra,* (intr. by Richard Simmons) Univ. of MN, Minneapolis, MN.

Despite significant shortages of cadaver donor organs for transplantation (TX), many TX centers remain reluctant to use related donors. This reluctance stems from concern not only over the physical risk to the donor, but also over the psychological risk. The purpose of this research is to investigate the psychological reactions of related donors 5-9 years post-TX. We interviewed (1) 133 related donors (1970-3 cohort) with quantitative measures pre-TX, and 5 days, 1 year, and now 5-9 years post-TX; (2) a control group of 65 "non-donors," i.e., family members who did not volunteer to donate a kidney. For 63% of the donors, their kidney is still functioning after 5-9 years ("successful donors"). Negative reactions to donation are rare and more common among unsuccessful than successful donors. Regret is slightly more common among unsuccessful donors (10% vs 5%) as are reports of post-TX difficulty in the relationship with the recipient (18% vs 5%, $p < .01$). There is indication of positive psychological reaction to donation among most donors. First, donors remain closer to recipients than do non-donors post-TX (5-9 years, % feeling "very close": 62% vs 37%, $p < .05$). Second, donors show higher self-esteem than non-donors post-TX ($p < .001$). Third, post-TX, donors are more likely to score favorably on a widely used measure of depressive-affect than they themselves pre-TX, than non-donor controls ($p < .001$) and than normal controls from large-scale surveys (N=1460,1501,2460). The % scoring favorably are:

DONORS			NON-DONORS		NORMAL CONTROLS
Pre-TX	Shortly Post	5-9 Years	Shortly Post	5-9 Years	
34%	60%	49%	26%	34%	30-37%

ACTIVATION OF ALLOIMMUNE MEMORY CELLS BY SOLUBLE FACTORS: A MODEL FOR ELICITATION OF SPECIFIC ALLOGRAFT RESPONSE BY IMMUNOLOGICALLY NON-SPECIFIC SIGNALS. M. Suthanthiran, A.L. Rubin, A. Novogrodsky*, and K.H. Stenzel. The New York Hospital - Cornell Medical Center, New York, New York.

The gene products of the major histocompatibility complex are primarily responsible for the induction of cytotoxic responses involved in the rejection of allografts. We report here that soluble products produced by mitogen-primed cells can effectively substitute for alloantigens and induce differentiation of alloimmune memory cells (memory cells) resulting in their acquisition of specific secondary cytolytic activity. Memory cells were generated in primary long-term unidirectional mixed lymphocyte cultures (MLC). Soluble factors were produced by exposing PBL to either neuraminidase (NA, 50 units/ml) and galactose oxidase (GO, 1.3 units/ml) for 30 min at 37°C or to sodium periodate (2 mM IO$_4^-$ for 30 min at 0°C). As expected, reexposure of memory cells to irradiated allogeneic cells (original priming stimulus) evoked brisk proliferative and specific secondary cytotoxic responses. More importantly, memory cells co-cultured with irradiated syngeneic cells in 30% soluble factors exhibited significant proliferation and specific secondary cytolytic activity. Our findings indicate a pathway for elicitation of specific allograft response by immunologically non-specific signals and provides a basis for the association between graft rejection and infection. Furthermore, the soluble factors appear to be the mediators by which cell to cell interactions resulting in the acquisition of differentiation is accomplished.

PRIMARY CADAVER RENAL TRANSPLANT IN DIABETIC RECIPIENTS: THE SEOPF PROSPECTIVE STUDY. Everett K. Spees, William K. Vaughn, D. Bernard Amos, G. Melville Williams. Johns Hopkins Univ., Balto., Md.

137 diabetics and 1138 nondiabetics received primary cadaver renal allografts during a 36 month period in the Southeastern Organ Procurement Foundation Prospective Study. Overall results to date: Graft Survival Rate (GSR)/Patient Survival Rate(PSR) ± SE (%)

Subgroup	N	6 months	12 months	24 months
Diabetic	137	50±5/89±3	46±5/83±4	38±6/75±7
Nondiabetic	1138	55±2/91±1	50±2/88±4	43±2/81±7

P values nonsignificant

When pretransplant blood transfusion (BT), antilymphocyte serum (ALS) treatment, and HLA match were considered, the highest GSR differences were noted in the following subgroups:

		Graft Survival Rates (%)					
Subgroup	N	BT	ALS	HLA	6 mo.	12 mo.	24 mo
Diabetic	14	Yes	Yes	High	57±15	57±15	57±15
Diabetic	6	No	No	Low	9±12	None	None
P value					.027		
Nondiabetic	75	Yes	Yes	High	69±6	66±6	66±6
Nondiabetic	47	No	No	Low	41±8	25±8	17±6
P value					.027	.001	.0003

For the total data BT accounted for a 29% increased GSR in diabetics, and 21% in nondiabetics. ALS accounted for 11-18% increased GSR in diabetics and 5-8% in nondiabetics. High HLA match gave a cumulative 15% GSR in diabetics at 24 months and 11% in nondiabetics ($p=.01$). The combination of any two of the factors BT, ALS or high HLA were additive, while the third factor was less than additive in GSR results. These data demonstrate that BT, ALS and high HLA match are dominant factors in primary cadaver renal allograft success in diabetics as well as nondiabetic recipients.

METABOLIC AND SCINTIGRAPHIC EVIDENCE OF DECREASED SECONDARY HYPERPARATHYROIDISM IN DIABETIC PATIENTS FOLLOWING TRANSPLANTATION AND AN APPARENT PROTECTIVE EFFECT FROM ASEPTIC NECROSIS. F.Vincenti, R.Hattner, W.Amend, N.Feduska, R.Duca, O.Salvatierra, University of California, San Francisco CA.

In a prospective study of 163 renal transplant patients (pts.), metabolic studies, including parathyroid hormone (PTH) and bone scintigraphy (Tc-99^m MDP) performed at time of transplantation were evaluated as possible predictors of avascular necrosis. Differences were noted between nondiabetic and diabetic pts.: (mean ± S.E.M.)

		Nondiabetic Pts.		Diabetic Pts.
Ca	mg%	9.7±0.1	p<.009	9.0±0.1
P	mg%	5.1±0.2	NS	5.0±0.4
Mag	mg%	2.9±0.1	NS	2.8±0.2
PHT	pg/ml	2959±196	p<.03	2088±320

Diabetic pts. had lower graded total skeletal scintigraphic scores than nondiabetic pts. (median 2.9 vs. 5.1, p<.0006). PTH levels showed positive correlations with bone scan scores (rho=.36, p<.001) and with alkaline phosphatase (r=.43, p<.00001) in nondiabetic but not in diabetic pts. Time on dialysis, proteinuria and duration of renal failure did not appear to account for these differences. In pts. at risk for >6 months (functioning graft and immunosuppressed), avascular necrosis occurred in 17% of nondiabetic pts. and only 2% of diabetic pts. (p <.04). Pts. with avascular necrosis had significantly higher PTH levels than pts. without avascular necrosis (4360±561 vs. 2679±197, p<.009). Thus, PTH levels directly relate to scintigraphic manifestation of hyperparathyroidism. The risk of avascular necrosis is clearly greater the higher the PTH levels pretransplant. The reduced hyperparathyroidism in diabetic pts. may confer protection from subsequent development of avascular necrosis.